Sedation and analgesia during intensive care after cardiac arrest

Ceric, Ameldina

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AMELDINA CERIC
DEPARTMENT OF CLINICAL SCIENCES LUND | LUND UNIVERSITY

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Ameldina Ceric

LUND
UNIVERSITY

DOCTORAL DISSERTATION

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Main supervisor:	Professor Niklas Nielsen
Co-supervisors:	Professor Tobias Cronberg
	Dr Anna Lybeck
	Dr Josef Dankiewicz
	Dr Teresa May
Faculty opponent:	Professor Ole Mathiesen, Department of Clinical Medicine, Anesthesiology and Intensive Care, Copenhagen University, Copenhagen, Denmark

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Abstract: Sedation and analgesia are commonly used during intensive care and targeted temperature management (TTM) after cardiac arrest to reduce anxiety, discomfort, and patient-ventilator asynchrony. However, there is limited evidence to guide clinicians in selecting optimal drugs and dosing strategies. While adequate sedation is necessary, deeper sedation may lead to adverse effects such as hemodynamic instability, compromised ventilation, delirium, and delayed awakening. The impact of sedation and analgesia on clinical outcomes including seizure occurrence, functional recovery, and survival, remains unknown.

Paper I This study evaluated sedation and analgesia practices after cardiac arrest between and within centers at 12-, 24-, and 48-hours following randomization to TTM at 33°C or 36°C. Associations with survival, clinical seizures, and delayed awakening were assessed in a cohort of 614 patients from 18 centers. Significant inter-center variability was identified in dosing and titration of sedatives and analgesics. Higher sedation and analgesia doses were associated with delayed awakening and clinical seizures, whereas downward titration of analgesics was associated with improved six-month survival.

Paper II This post hoc analysis of 1861 patients from the TTM2-trial investigated the associations between sedation and analgesia use and functional outcomes, survival, clinical seizures, and delayed awakening. Cumulative doses of sedatives and analgesics such as propofol, midazolam, fentanyl, and remifentanil were analyzed up to 72 hours after randomization to hypothermia or normothermia. Higher propofol doses and the use of remifentanil/fentanyl were associated with both good functional outcomes and survival, as well as increased occurrence of clinical seizures and delayed awakening, analyzed in multivariable logistic regression model adjusting for severity of illness and clinical factors influencing sedation.

Paper III This TTM2 substudy investigated the impact of hypothermia versus normothermia on sedative and analgesic serum concentrations and time to awakening. Blood samples and cumulative dosing data were collected at the end of TTM and at 72 hours (end of protocolized fever prevention) and analyzed for propofol, midazolam, clonidine, dexmedetomidine, morphine, oxycodone, ketamine, and esketamine concentrations. Among 71 patients (33 treated with hypothermia, 38 with normothermia), no significant differences in cumulative drug doses or serum concentrations were observed between groups. While hypothermia prolonged awakening in midazolam-treated patients, overall awakening times did not significantly differ. These findings suggest that hypothermia does not significantly alter sedative pharmacokinetics, though larger studies are needed to confirm these results.

Paper IV This systematic review, meta-analysis, and trial sequential analysis (TSA) investigated the effects of sedation depth on mortality, serious adverse events, neurological outcome, and delirium in critically ill adults. Fifteen randomized clinical trials (4352 participants) were analyzed. No significant differences were observed between deeper and lighter sedation in terms of mortality, delirium incidence, or serious adverse events. TSA indicated futility in detecting further mortality differences. While results were robust, moderate-quality evidence underscore the need for high-quality studies with higher methodological rigor.

Paper V This study protocol describes the SED-CARE trial, a randomized, international, multicenter study investigating the effects of sedation depth on six-month mortality in comatose survivors of out-of-hospital cardiac arrest. Adults who remain comatose after sustained return of spontaneous circulation will be randomized within four hours to either deep (Richmond agitation and sedation scale (RASS) -4/-5) or minimal sedation (RASS 0 to -2) for 36 hours. Conducted as part of the Sedation, Temperature and Pressure after Cardiac Arrest and Resuscitation factorial trial, which also investigates temperature control and blood pressure strategies after cardiac arrest. A total of 3500 participants will be enrolled, based on a power calculation designed to detect an absolute risk reduction of 5.6%, with an alpha of 0.05 and 90% power. Findings from this large-scale study are expected to inform future guidelines and optimize post-cardiac arrest care.

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Ameldina Ceric

LUND
UNIVERSITY

Faculty of Medicine

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To my beloved family, Eldar and Emin

"He takes the souls at the time of their death, and those that do not die He takes during their sleep. Then He keeps those for which He has decreed death and releases the others for a specified term. Surely in this are signs for people who reflect" – Ruh

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Abstract

Sedation and analgesia are commonly used during intensive care and targeted temperature management (TTM) after cardiac arrest to facilitate TTM and reduce anxiety, discomfort, and patient-ventilator asynchrony. However, there is limited evidence to guide clinicians in selecting optimal drugs and dosing strategies. While adequate sedation may be necessary, deeper sedation may lead to adverse effects such as hemodynamic instability, compromised ventilation, delirium, and delayed awakening. The impact of sedation and analgesia on clinical outcomes including seizure occurrence, functional recovery, and survival, remains unknown.

Paper I

This study evaluated sedation and analgesia practices after cardiac arrest between and within centers at 12-, 24-, and 48-hours following randomization to TTM at 33°C or 36°C. Associations with survival, clinical seizures, and delayed awakening were assessed in a cohort of 614 patients from 18 centers. Significant inter-center variability was identified in dosing and titration of sedatives and analgesics. Higher sedation and analgesia doses were associated with delayed awakening and clinical seizures, whereas downward titration of analgesics was associated with improved six-month survival.

Paper II

This post hoc analysis of 1,861 patients from the TTM2-trial investigated the associations between sedation and analgesia use and functional outcomes, survival, clinical seizures, and delayed awakening. Cumulative doses of sedatives and analgesics such as propofol, midazolam, fentanyl, and remifentanil were analyzed up to 72 hours after randomization to hypothermia or normothermia. Higher propofol doses and the use of remifentanil/fentanyl were associated with both good functional outcomes and survival, as well as increased occurrence of clinical seizures and delayed awakening, analyzed in multivariable logistic regression model adjusting for severity of illness and clinical factors influencing sedation.

Paper III

This TTM2 substudy investigated the impact of hypothermia versus normothermia on sedative and analgesic serum concentrations and time to awakening. Blood samples and cumulative dosing data were collected at the end of TTM and at 72 hours (end of protocolized fever prevention) and analyzed for propofol, midazolam, clonidine, dexmedetomidine, morphine, oxycodone, ketamine, and esketamine concentrations. Among 71 patients (33 treated with hypothermia, 38 with normothermia), no significant differences in cumulative drug doses or serum concentrations were observed between groups. While hypothermia was associated with prolonged awakening in midazolam-treated patients, overall awakening times

did not significantly differ between the two groups. These findings suggest that hypothermia does not significantly alter sedative pharmacokinetics, though larger studies are needed to confirm these results.

Paper IV

This systematic review, meta-analysis, and trial sequential analysis (TSA) investigated the effects of sedation depth on mortality, serious adverse events, neurological outcome, and delirium in critically ill adults. Fifteen randomized clinical trials (4352 participants) were analyzed. No significant differences were observed between deeper and lighter sedation in terms of mortality, delirium incidence, or serious adverse events. TSA indicated futility in detecting mortality differences of 16% or more. While results were robust, moderate-quality evidence underscore the need for high-quality studies with higher methodological rigor.

Paper V

This study protocol describes the SED-CARE trial, a randomized, international, multicenter study investigating the effects of sedation depth on six-month mortality in comatose survivors of out-of-hospital cardiac arrest. Adults who remain comatose after sustained return of spontaneous circulation will be randomized within four hours to either deep (Richmond agitation and sedation scale (RASS) -4/-5) or minimal sedation (RASS 0 to -2) for 36 hours. Conducted as part of the *Sedation, Temperature and Pressure after Cardiac Arrest and Resuscitation* (STEPCARE) factorial trial, which also investigates temperature control and blood pressure strategies after cardiac arrest. A total of 3500 participants will be enrolled, based on a power calculation designed to detect an absolute risk reduction of 5.6%, with an alpha of 0.05 and 90% power. Findings from this large-scale study are expected to inform future guidelines and optimize post-cardiac arrest care.

List of publications

This thesis if based on the following original scientific papers, referred to int the text by their Roman numerals.

I. **Ceric A**, May TL, Lybeck A, Cronberg T, Seder DB, Riker RR, Hassager C, Kjaergaard J, Haxhija Z, Friberg H, Dankiewicz J, Nielsen N. Cardiac Arrest Treatment Center Differences in Sedation and Analgesia Dosing During Targeted Temperature Management. Neurocrit Care. 2023 Feb;38(1):16-25.

II. **Ceric A**, Dankiewicz J, Cronberg T, Düring J, Moseby-Knappe M, Annborn M, May TL, Thomas M, Grejs AM, Rylander C, Belohlavek J, Wendel-Garcia P, Haenggi M, Schrag C, Hilty MP, Keeble TR, Wise MP, Young P, Taccone FS, Robba C, Cariou A, Eastwood G, Saxena M, Ullén S, Lilja G, Jakobsen JC, Lybeck A, Nielsen N. Sedation and analgesia in post cardiac arrest care: a post hoc analysis of the TTM2 trial. *(Under peer review in Critical Care).*

III. Annborn M, **Ceric A**, Borgquist O, During J, Moseby-Knappe M, Lybeck A. Hypothermia versus normothermia after out-of-hospital cardiac arrest; the effect on post-intervention serum concentrations of sedatives and analgesics and time to awakening. Resuscitation. 2023 Jul;188:109831.

IV. **Ceric A**, Holgersson J, May TL, Skrifvars MB, Hästbacka J, Saxena M, Aneman A, Delaney A, Reade MC, Delcourt C, Jakobsen JC, Nielsen N. Effect of level of sedation on outcomes in critically ill adult patients: a systematic review of clinical trials with meta-analysis and trial sequential analysis. EClinicalMedicine. 2024 Mar 28;71:102569.

V. **A. Ceric,** J. Dankiewicz, J. Hästbacka, P. Young, V. H. Niemelä, F. Bass, M. B. Skrifvars, N. Hammond, M. Saxena, H. Levin, G. Lilja, M. Moseby-Knappe, M. Tiainen, M. Reinikainen, J. Holgersson, C. B. Kamp, M. P. Wise, P. J. McGuigan, J. White, K. Sweet, T. R. Keeble, G. Glover, P. Hopkins, C. Remmington, J. M. Cole, N. Gorgoraptis, D. G. Pogson, P. Jackson, J. Düring, A. Lybeck, J. Johnsson, J. Unden, A. Lundin, J. Kåhlin, J. Grip, E. M. Lotman, L. Romundstad, P. Seidel, P. Stammet, T. Graf, A. Mengel, C. Leithner, J. Nee, P. Druwé, K. Ameloot, A. Nichol, M. Haenggi, M. P. Hilty, M. Iten, C. Schrag, M. Nafi, M. Joannidis, C. Robba, T. Pellis, J. Belohlavek, D. Rob, Y. M. Arabi, S. Buabbas, C. Yew Woon, A. Aneman, A. Stewart, M. Reade, C. Delcourt, A. Delaney, M. Ramanan, B. Venkatesh, L. Navarra, B. Crichton, A. Williams, D. Knight, J. Tirkkonen, T. Oksanen, T. Kaakinen, S. Bendel, H. Friberg, T. Cronberg, J. C. Jakobsen, N. Nielsen. Continuous deep sedation versus minimal sedation after cardiac arrest and resuscitation (SED-CARE): A protocol for a randomized clinical trial. Acta Anaesthesiol Scand. 2025; 69(5):e70022. doi:10.1111/aas.70022.

Publications not included in thesis

I. Holgersson J, **Ceric A**, Sethi N, Nielsen N, Jakobsen JC. Fever therapy in febrile adults: systematic review with meta-analyses and trial sequential analyses. BMJ. 2022 Jul 12;378:e069620.

II. **Ceric A**, Holgersson J, May T, Skrifvars MB, Hästbacka J, Saxena M, Aneman A, Delaney A, Reade MC, Delcourt C, Jakobsen J, Nielsen N. Level of sedation in critically ill adult patients: a protocol for a systematic review with meta-analysis and trial sequential analysis. BMJ Open. 2022 Sep 8;12(9):e061806.

III. Haxhija Z, Seder DB, May TL, Hassager C, Friberg H, Lilja G, **Ceric A**, Nielsen N, Dankiewicz J. External validation of the CREST model to predict early circulatory-etiology death after out-of-hospital cardiac arrest without initial ST-segment elevation myocardial infarction. BMC Cardiovasc Disord. 2023 Jun 20;23(1):311.

IV. **Ceric, A**, Wise MP. Optimal sedation in the patients with acute brain injury including post cardiac arrest. Review for Critical Care Clinics of North America. CCC 41.4 (Shehabi/Stollings/Girard) Optimizing Sedation & Analgesia in the ICU, Chapter 12.

Abbreviations

AED	Antiepileptic drugs
ATP	Adenosine triphosphate
CAG	Coronary angiography
CI	Confidence interval
CPC	Cerebral performance category
CPR	Cardiopulmonary resuscitation
DSMC	Data and safety monitoring committee
ECG	Electrocardiography
ECMO	Extracorporeal membrane oxygenation
EEG	Electroencephalography
ICP	Intracranial pressure
ICU	Intensive care unit
FOUR	Full outline of unresponsiveness
GCS	Glasgow coma scale
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
MAP	Mean arterial pressure
mRS	Modified Rankin scale
NMB	Neuromuscular blockade
OHCA	Out-of-hospital cardiac arrest
OR	Odds ratio
Rob2	Risk of bias tool 2
ROSC	Return of spontaneous circulation
PCAS	Post cardiac arrest syndrome
PCI	Percutaneous coronary angiography
RASS	Richmond agitation-sedation scale
RCT	Randomized clinical trial
RR	Risk ratio
SAE	Serious adverse events
SAS	Riker sedation-agitation scale
SED-CARE	Sedation after Cardiac arrest and Resuscitation
STEPCARE	Sedation, Temperature, and Pressure after Cardiac arrest and Resuscitation
TTM	Targeted temperature management
TTM-trial	Targeted temperature management trial
TTM2-trial	Targeted temperature management 2 trial
TSA	Trial sequential analysis
WLST	Withdrawal of life sustaining therapy

Thesis at a glance

Title	Aim	Methods	Results
Paper I: Cardiac Arrest Treatment Center Differences in Sedation and Analgesia Dosing During Targeted Temperature Management	Evaluate sedation and analgesia practices in TTM at 33°C vs 36°C and assess associations with survival, seizures, and awakening.	Multicenter observational study analyzing 614 patients from 18 centers. Drug selection, dosing, and titration were compared in multivariable linear regression model.	Significant variability in sedation practices across centers. Higher sedation/analgesia doses associated with delayed awakening and seizures, and downward titration of analgesics with improved survival.
Paper II: Sedation and analgesia in post-cardiac arrest care: a post hoc analysis of the TTM2-trial	Investigate associations between sedation/analgesia use and functional outcome, survival, seizures, and awakening in TTM2-trial.	Post hoc analysis of 1861 patients in TTM2-trial. Multivariable logistic regression used to adjust for severity of illness.	Higher propofol doses and fentanyl/remifentanil use were associated with survival, and good functional outcome, and increased seizures/delayed awakening.
Paper III: Hypothermia versus normothermia after out-of-hospital cardiac arrest; the effect on postintervention serum concentrations of sedatives and analgesics and time to awakening	Examine the impact of hypothermia vs normothermia on sedative and analgesic serum concentrations and time to awakening.	TTM2 substudy measuring drug serum concentrations and awakening time in 71 patients in multivariable regression model.	No significant differences in drug concentrations between hypothermia and normothermia groups. Awakening was prolonged with midazolam use.
Paper IV: Effect of level of sedation on outcomes in critically ill adult patients: a systematic review of clinical trials with meta-analysis and trial sequential analysis	Assess effects of sedation depth on mortality, serious adverse events (SAE), and delirium in critically ill adults.	Systematic review, meta-analysis, and trial sequential analysis (TSA) of 15 randomized clinical trials (RCTs) (4352 participants) comparing deep vs light sedation outcomes.	No significant mortality, SAE, or delirium differences between different sedation levels. TSA suggested futility in detecting mortality differences.
Paper V: Continuous deep sedation versus minimal sedation after cardiac arrest: A study protocol for a randomized clinical trial	Describe protocol for SED-CARE trial investigating sedation depth impact on six-month mortality in OHCA patients.	RCT trial enrolling 3500 patients to assess sedation depth impact on six-month mortality.	Study ongoing. Expected to inform guidelines and optimize sedation and analgesia strategies in post-cardiac arrest care based on a large-scale sample.

Introduction

Cardiac arrest

Cardiac arrest is a critical event defined by the sudden cessation of cardiac mechanical activity, typically identified by the absence of circulation signs, unresponsiveness, and cessation of breathing, often confirmed as pulselessness by trained personnel [1, 2]. This condition leads to the rapid loss of blood flow to vital organs, making immediate intervention essential to prevent death. While cardiopulmonary resuscitation (CPR) can temporarily restore circulation, addressing the underlying causes is vital for long-term survival. Cardiac arrest represents the third leading cause of death in Europe and remains a significant global health challenge, demanding attention from healthcare providers, researchers, and policymakers [3-5].

Despite its high mortality rates, advancements in resuscitative techniques, early intervention strategies, and a deeper understanding of its pathophysiology have contributed to improving outcomes [6-8]. This background chapter describes the epidemiology, mechanisms, current management strategies, and the need for innovative approaches to enhance survival rates and improve long-term outcomes post-cardiac arrest. Among these management strategies, sedation and analgesia have crucial role in optimizing post-cardiac arrest care, yet their practices remain highly variable and insufficiently studied. This dissertation aims to investigate sedation and analgesia practices in this context, contributing to ongoing research and driving advancements in clinical practices to improve patient outcomes.

Background

Location and causes of cardiac arrest

Cardiac arrest is typically classified based on its location of occurrence as either out-of-hospital cardiac arrest (OHCA) or in-hospital cardiac arrest [2, 9]. This distinction reflects perceived differences in underlying causes, response times, and available interventions; however, recent evidence suggests that differences in outcomes may be smaller than previously assumed [10-12]. Studies indicate that in-hospital cardiac arrest patients are more often female, have a higher burden of

comorbidities, and are more likely to experience arrest due to non-cardiac causes, such as respiratory failure and sepsis [11, 12]. In contrast, OHCA is primarily of medical origin (90%), with cardiac causes being the most prevalent, followed by respiratory and neurological causes [3, 13-15]. Non-medical causes include trauma, suicide, drug overdose, and other external factors. Furthermore, cardiac arrest can be categorized based on the first documented rhythm as either shockable (ventricular tachycardia or ventricular fibrillation) or non-shockable rhythm. Shockable rhythms occur in approximately 20% of cases and are associated with more favorable outcomes [16, 17].

Epidemiology of cardiac arrest

OHCA is a major public health concern, affecting approximately 700,000 people annually in Europe and the US [18-21]. Cardiovascular disease, the leading underlying cause of cardiac arrest, remains the primary global cause of death, with mortality rising from 6.9 million to 8.9 million deaths in 2000 to 2019 [22]. The incidence of OHCA varies by region and reporting system. In Europe, the overall incidence is approximately 89 per 100,000 individuals (varying from 53 to 166) though this differs across countries, for example, 55 per 100,000 in the United Kingdom, 93 per 100,000 in Denmark, and around 50 per 100,000 in Sweden [8, 13, 23-26]. Survival to hospital discharge has improved in recent years, currently averaging 9% in Europe and the US, with variations ranging from 3% to 20%. For instance, survival rates are 8% in the UK and 12% in Sweden [3, 8, 26-28]. This increase is largely attributed to higher rates of bystander CPR and greater public access to early defibrillation [26, 28-30].

Chain of survival

The “chain of survival” is a structured framework developed to improve outcomes for cardiac arrest victims and provides a simple means to educate the public [31]. It consists of four key steps: early recognition and activation of emergency services, early CPR, early defibrillation, and post-resuscitation care (see Figure 1). When implemented effectively, this sequence can significantly improve survival rates [32]. Among these steps, early recognition and bystander CPR have the greatest impact on survival, as the number of patients who survive decreases at each subsequent stage [33]. In recent years, bystander CPR rates have risen to between 30% and 58%, though substantial variation exists between countries [4, 26]. While early interventions are critical, post resuscitation care (also named post-cardiac arrest care), the final step in the chain of survival, is increasingly recognized as essential for improving survival and long-term recovery [34, 35].

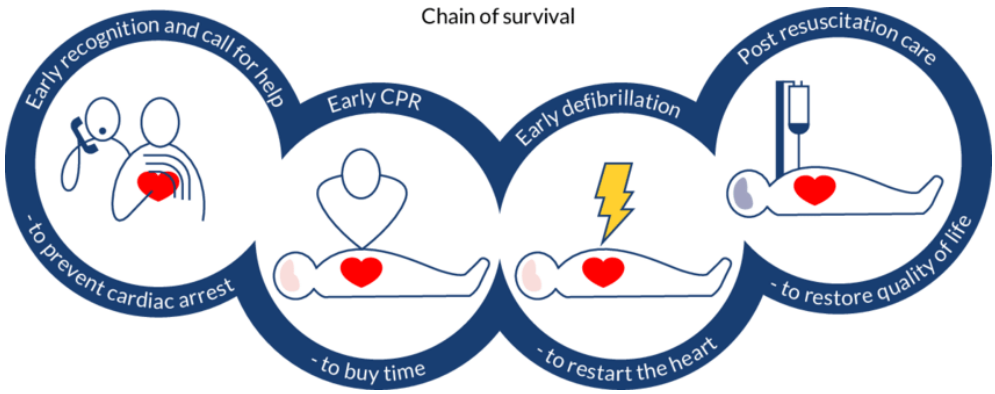

Figure 1
The Chain of survival, conceptual illustration of survival after cardiac arrest dependent on critical interlinked interventions. © European Resuscitation Council, reprinted with permission.

Post cardiac arrest syndrome

Cardiac arrest, the sudden cessation of blood flow, deprives vital organs, particularly the heart and brain, of oxygen and glucose, leading to severe metabolic and cellular stress [36]. Resuscitation efforts, including CPR and ROSC, aim to re-establish perfusion and limit ischemic damage. However, the subsequent ischemia-reperfusion injury triggers a cascade of pathophysiological responses, activating immune and coagulation pathways [37, 38]. This inflammatory and pro-thrombotic response contributes to multiple organ dysfunction, collectively known as post-cardiac arrest syndrome (PCAS). PCAS manifests as a spectrum of multiorgan failure and neurological impairment that develops within hours to days after cardiac arrest. It includes post-cardiac arrest hypoxic-ischemic brain injury, myocardial dysfunction, systemic ischemia-reperfusion response, and persistent precipitating pathology (see Table 1) [39]. Similar to sepsis, PCAS is characterized by systemic inflammation, leading to endothelial damage, microcirculatory dysfunction, intravascular volume depletion, and vasodilation [40-42]. These complications can hinder recovery, impact long-term outcomes, and significantly contribute to morbidity and mortality following cardiac arrest [39, 43]. The severity of PCAS depends on the duration of ischemia, the underlying cause of cardiac arrest, and pre-existing comorbidities, all of which influence the extent of organ dysfunction and neurological injury [39, 44].

Table 1. Schematic illustration of the four components of the post-cardiac arrest syndrome, their pathophysiology and clinical manifestations according to the International Liaison Committee on Resuscitation.

Post cardiac arrest syndrome			
	Pathophysiology	Clinical manifestations	Management
Brain injury	Cerebrovascular dysfunction: Impaired autoregulation, ischemia-reperfusion injury. Neurological damage: Cerebral oedema, neuronal death through gliosis and apoptosis.	Impaired consciousness, seizures/myoclonus, neurocognitive dysfunction, electroencephalography (EEG), suppression, stroke, brain death.	Targeted temperature management, EEG monitoring, seizure treatment, blood pressure management
Myocardial dysfunction	Global hypokinesis, reduced cardiac output, acute coronary syndrome.	Dysrhythmias, cardiovascular collapse, hypotension	Revascularization, hemodynamic optimization (e.g. intravenous fluids, inotropes, intraaortic balloon counterpulsation, left ventricular assist device, extracorporeal membrane oxygenation)
Systemic/ischemic reperfusion response	Systemic inflammatory response, cytokine release, inflammatory mediators, impaired vasoregulation and coagulation, adrenal suppression, impaired tissue oxygenation and immune function, aspiration pneumonia.	Tissue hypoxia/ischemia, cardiovascular collapse, hypotension, fever, hypoglycemia, infection, multi-organ failure.	Oxygenation, infection control, organ support.
Persistent precipitating physiology	Common causes: cardiomyopathy, acute coronary syndrome, asthma, chronic obstructive pulmonary disease, cerebrovascular accident, pulmonary embolism, hypoxemia, acidosis, sepsis, pneumonia, hemorrhage, dehydration.	Clinical manifestation according to etiology.	Treatment according to underlaying cause.

Post cardiac arrest care treatment

Critical care for unconscious OHCA patients includes hemodynamic support, mechanical ventilation, temperature management, treatment of seizures, and potential coronary angiography if cardiac etiology is suspected [34, 43]. Tracheal intubation is typically performed during or shortly after CPR to facilitate oxygenation, ventilation monitoring, and aspiration protection [45-47]. Depending on the patient's level of consciousness post-ROSC, sedation and analgesia may be necessary [45-47]. Following cardiac arrest, patients are at risk of hypoxic-ischemic brain injury and organ dysfunction. While increased blood oxygenation can enhance cerebral oxygen delivery, excess oxygen may generate harmful oxygen radicals [48, 49]. Current evidence supports initial administration of 100% inspired oxygen, followed by titration to maintain normal oxygen saturation (92-98%) once levels can be reliably monitored [45, 47, 50-54]. Carbon dioxide plays a crucial role in cerebrovascular tone and cerebral blood flow regulation, and this cerebrovascular reactivity appears to be preserved post-cardiac arrest [52, 55, 56]. Guidelines recommend targeting normocapnia, however this may be insufficient to restore cerebral blood flow after cardiac arrest. While observational studies suggest potential benefits of mild hypercapnia, recent randomized clinical trials (RCTs) have not confirmed these findings [57-59].

Post cardiac arrest syndrome: Myocardial dysfunction

Cardiovascular failure is the leading cause of death within the first three days following cardiac arrest [21, 60]. Significant myocardial dysfunction is common post-arrest, typically improving within 2–3 days, though full recovery may take longer [61, 62]. In patients with ST-elevation post-ROSC, immediate percutaneous coronary intervention (PCI) is crucial, as myocardial ischemia-induced arrhythmia is a frequent cause of sudden cardiac death. Early PCI significantly improves survival and neurological outcomes, with over 80% of patients with ST-elevation or left bundle branch block on electrocardiography (ECG) having an acute coronary lesion [63]. Current guidelines recommend emergency cardiac catheterization for these patients [43].

For patients without ST-elevation, recent coronary occlusion cannot be ruled out, and the need for early coronary angiography (CAG) should be assessed based on hemodynamic or electrical instability and ongoing myocardial ischemia [64]. Key factors in this decision include medical history, pre-arrest symptoms, initial cardiac rhythm, post-ROSC ECG, and echocardiography findings. When ischemia is suspected, early CAG is recommended, whereas in low-probability cases, delayed CAG allows for initial intensive care unit (ICU) stabilization and post-resuscitation care. Studies have shown no significant difference in survival or functional outcomes between early and delayed CAG in patients without ST-elevation [65-67].

Observational studies suggest hypotension is associated with poor outcomes. However, meta-analyses of randomized clinical trials comparing lower and higher mean arterial pressure (MAP) targets have not shown significant differences in mortality or functional outcomes [68-77]. Hemodynamic monitoring and management are essential due to the frequent occurrence of post-resuscitation myocardial dysfunction, with early echocardiography guiding treatment [45-47]. Current recommendations suggest setting hemodynamic goals, including MAP and systolic blood pressure targets, but there is insufficient evidence on the optimal hemodynamic threshold [77, 78]. MAP is a key determinant of cerebral blood flow, and higher MAP targets may be required in brain-injured patients to improve cerebral perfusion and mitigate hypoxic-ischemic brain injury, particularly in the presence of cerebral swelling and increased intracranial pressure (ICP) [78, 79]. Additionally, cerebral autoregulation is often impaired post-cardiac arrest, making cerebral blood flow more dependent on MAP at lower levels, thereby increasing the risk of cerebral hypoperfusion and secondary brain injury [78-80]. Post-resuscitation myocardial dysfunction often requires inotropic support, as vasodilation and vasoplegia in PCAS driven by systemic inflammation and myocardial dysfunction, can lead to circulatory collapse. While vasopressors and inotropes have dose-dependent adverse effects, pilot studies suggest noradrenaline is well tolerated even at higher MAP targets in post-cardiac arrest patients [81, 82]. Dobutamine is the most established inotropic agent to increase cardiac output. When fluids, inotropes, and vasopressors fail to maintain circulation, mechanical circulatory support devices (e.g., intra-aortic balloon counterpulsation, left ventricular assist device, extracorporeal membrane oxygenation (ECMO)) may be considered.

Post-cardiac arrest brain injury

Post-cardiac arrest hypoxic-ischemic brain injury refers to the neurological damage that occurs following successful resuscitation [83]. Among the patients initially resuscitated from OHCA and who die, approximately two thirds of deaths result from withdrawal of life-sustaining therapy (WLST) following an assessment of brain injury and a prognosticated poor neurological outcome [21, 84, 85]. Consequently, post-cardiac arrest care prioritizes strategies to mitigate brain injury, as understanding its mechanisms and implications is essential to optimize survival and neurological recovery.

The brain, despite constituting only about 2% of total body weight, accounts for approximately 15% of total metabolism due to the high energy demands of its neurons and glial cells [86]. Glial cells provide structural and regulatory support, while neurons communicate via electrical impulses, neurotransmitter exocytosis, and reuptake, processes that require adenosine triphosphate (ATP). Neuronal metabolic demand can double during periods of high activity, making these cells

particularly vulnerable to oxygen and glucose depletion when blood flow is interrupted.

Post-cardiac arrest hypoxic-ischemic brain injury involves multiple complex mechanisms, including endothelial and microvascular damage, which disrupts blood flow and oxygen delivery, leading to tissue hypoxia. Within 2–3 minutes of circulatory arrest, cessation of blood flow to the brain results in mitochondrial dysfunction, ATP depletion, and failure of energy-dependent Na^+/K^+ pumps, leading to loss of membrane potential and anoxic depolarization [87, 88]. ATP depletion also causes extracellular accumulation of neurotransmitters and intracellular Ca^{2+} overload, further exacerbating neuronal injury and cell death [87, 88]. These mechanisms trigger widespread neuronal damage, with most injury occurring within the first 72 hours. Additionally, neuroinflammation, a secondary immune response to the initial insult, can exacerbate neuronal damage and contribute to long-term neurological dysfunction [89]. The post cardiac arrest hypoxic-ischemic brain injury can present clinically as loss of consciousness, seizures, myoclonus, neurocognitive dysfunction, EEG suppression, and ultimately brain death [90, 91].

Seizures

Seizures occur in approximately one-third of cardiac arrest patients in the ICU, often indicating severe hypoxic–ischemic brain injury [92]. They may present as clinical convulsions or abnormal EEG activity, with continuous EEG monitoring revealing substantial overlap between the two [93]. Seizure activity can be focal, multifocal, or generalized, affecting various body regions.

Myoclonic seizures are the most common post-cardiac arrest, characterized by sudden, brief muscle contractions typically appearing within the first 24-48 hours. They are strongly associated with poor prognosis and often exhibit epileptiform activity on EEG, such as synchronous time-locked discharges or burst-suppression [93-95]. Status myoclonus, defined as a severe and continuous form of myoclonus lasting more than 30 minutes, occurs in about 20% of patients and is associated with a poor prognosis if it develops within 48 hours post–cardiac arrest [94, 96, 97].

Subcortical myoclonus is a distinct subgroup of myoclonic seizures that originates from subcortical structures (e.g. brainstem or basal ganglia) rather than the cerebral cortex. Unlike cortical myoclonus, subcortical myoclonus is not consistently associated with cortical EEG findings. This distinction is important, as subcortical myoclonus is not necessarily linked to poor outcomes [97].

Lance-Adams syndrome is a form of generalized action myoclonus, that typically develops days to weeks after cardiac arrest, often persisting chronically with preserved consciousness. Early prognostication is challenging, as affected patients may initially be indistinguishable from those with post-cardiac arrest myoclonus

who ultimately have poor outcomes. Additionally, sedation used in post-cardiac arrest care can mask early signs of Lance-Adams syndrome, further complicating accurate assessment and prognosis [98, 99].

Tonic-clonic seizures and combined seizures are less commonly observed and are not necessarily associated with poor outcome [92].

Seizures can exacerbate brain injury by increasing metabolic demand. Management typically involves antiepileptic drugs (AEDs) such as levetiracetam and valproate. Current guidelines recommend against prophylactic AED use in post-cardiac arrest patients but support active seizure treatment when detected [43, 47]. A recent study in comatose cardiac arrest survivors found that suppressing rhythmic and periodic EEG activity with antiseizure medication for at least 48 hours did not significantly improve neurologic outcomes at 3 months compared to standard care alone [100]. Sedatives, some of which are also potent antiepileptic agents, may mitigate secondary brain injury and optimize neurological recovery by lowering metabolic rate and ICP [101, 102]. In clinical practice, sedation is often increased when a patient is having clinical seizures or shows signs of pain and agitation. However, sedation and analgesia during targeted temperature management (TTM) and post-cardiac arrest care may mask clinical seizures, making EEG monitoring essential for accurate detection and prognostication [43, 47].

Targeted temperature management

Fever, defined as an elevated body temperature due to a raised hypothalamic setpoint caused by pyrogens in response to inflammation and infection, is part of the body's natural defense mechanism [103, 104]. While it can inhibit certain pathogens and enhance immune activity, both fever and hyperthermia are hypothesized to lead to adverse effects such as increased metabolic demand, seizures, and organ damage [104]. In hospital settings, fever management is standard practice to reduce discomfort and physiological stress. In ICU, fever therapy aims to lower metabolic demand and prevent hypoxic-ischemic tissue injury.

Early studies in 2002 demonstrated that inducing hypothermia (32–34°C) improved outcomes for patients with shockable rhythms following cardiac arrest [105, 106]. However, subsequent trials, including the Target Temperature Management trial (TTM-trial) and Target Temperature Management 2 trial (TTM2-trial), found no significant benefits of hypothermia over maintaining normothermia [107, 108]. As a result, the American Heart Association guidelines currently recommend maintaining temperatures between 32°C and 37.5°C for 24 hours [109]. Similarly, the European Society for Emergency Medicine and the European Society of Anaesthesiology and Intensive Care emphasize temperature control as a key component of post-cardiac arrest care, but rather than promoting strict hypothermia

protocols, they now recommend preventing hyperthermia (>37.7°C) for at least 72 hours due to insufficient evidence supporting specific temperature targets [110, 111]. Additionally, TTM is resource-intensive and carries potential risks, including arrhythmias that compromise cardiac stability, coagulation disturbances that increase the risk of hemorrhage and thromboembolism, and may increase the risk of infections and sepsis.

Sedation and analgesia

Sedation and analgesia are essential parts of critical care management, alleviating anxiety, discomfort, and pain while facilitating mechanical ventilation, invasive procedures, and other treatments necessary for critically ill patients. However, their use requires a balance between ensuring patient comfort and minimizing adverse effects. Deeper sedation can compromise circulatory and respiratory function, prolong mechanical ventilation, delay awakening, and increase the risk of delirium [112].

Sedation strategies

Lighter sedation strategies in general ICU populations have been associated with shorter time to extubation, reduced ICU length of stay, and a lower incidence of delirium [113, 114]. However, there is no universally accepted definition of “light sedation”, and different approaches, including protocolized sedation, goal-directed sedation, and daily sedation interruptions, are commonly used. Sedation depth is typically monitored using validated assessment tools, such as the Richmond Agitation-Sedation Scale (RASS) and the Riker Sedation-Agitation Scale (SAS), which are widely applied in critically ill patients [115, 116].

Table 2. Richmond Agitation and Sedation Scale (RASS).

RASS	Classification	Description
+4	Combatative	Overtly combative, violent, danger to staff
+3	Very agitated	Pulls or removes tubes/catheters; aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious, apprehensive, but not aggressive
0	Alert and calm	Normal responsiveness
-1	Drowsy	Awakens to voice (eye opening/contact) > 10 seconds
-2	Light sedation	Briefly awakens to voice (eye opening/contant) < 10 seconds
-3	Moderate sedation	Movement or eye opening, no eye contact
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Table 3. Riker Sedation-Agitation Scale (SAS).

SAS	Classification	Description
7	Dangerous Agitation	Pulling at endotracheal tube, attempting to climbing over bedrail, striking at staff, thrashing
6	Very Agitated	Requiring restraint and frequent verbal reminding of limits, biting endotracheal tube
5	Agitated	Anxious or physically agitated, calms to verbal instructions
4	Calm and cooperative	Calm, easily arousable, follows commands
3	Sedated	Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again
2	Very Sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands

Both RASS and SAS are validated tools for assessing sedation in general ICU populations. However, their applicability in patients with acute brain injury or post-cardiac arrest syndrome is limited, as these patients are often excluded from validation studies due to brain injury-induced unresponsiveness, which confounds the assessment of sedation depth. Observational studies suggest a potential mortality benefit from lighter sedation strategies, but RCTs have shown inconsistent results [114, 117-119]. Additionally, non-sedation strategies for mechanically ventilated ICU patients have been explored in RCTs, demonstrating feasibility but no significant differences in clinical outcomes [120].

Sedation strategies in patients with acute brain injury

In patients with acute brain injury, sedation and analgesia play a critical role in maintaining cerebral perfusion pressure (CPP) and ICP, managing seizures, and preventing secondary brain injury [121, 122]. However, sedation can obscure neurological assessments, making it difficult to accurately evaluate consciousness level, pupillary response, motor function, and EEG activity. These risks are particularly pronounced in patients with acute brain injuries or hypoxic-ischemic encephalopathy following cardiac arrest and presents unique challenges in the ICU. This is particularly relevant for patients undergoing TTM, where sedation is essential to control shivering and alleviate discomfort, as shivering increases body temperature and metabolic demand and may exacerbate neurological injury [123].

Patients with acute brain injury are often excluded from sedation trials due to their unique pathophysiological considerations, including the need to manage primary injury, prevent secondary brain injury, and mitigate confounding effects on neurological assessments [124]. While general ICU guidelines favor lighter sedation strategies to reduce mechanical ventilation duration and ICU length of stay, patients with acute brain injury, such as traumatic brain injury (TBI) and stroke, often require deeper sedation to manage CPP and ICP [125-127]. In these patients, sedation is primarily used to control agitation, facilitate mechanical ventilation, and prevent secondary brain injury by maintaining ICP and CPP within optimal ranges [128]. Regular neurological assessments are essential, necessitating the use of short-acting sedatives to allow for frequent clinical evaluations. Similarly, in acute ischemic stroke, excessive sedation can mask evolving neurological deficits and delay necessary interventions [129]. Additionally, pain management in these patients is also critical, as pain can elevate ICP, but analgesics must be carefully administered to avoid deeper sedation.

For post-cardiac arrest patients, sedation is essential during TTM to suppress shivering and alleviate discomfort, reduce metabolic demand, and facilitate mechanical ventilation [45, 47]. Unlike TBI and stroke, where deep sedation may be necessary for ICP control, post-cardiac arrest sedation strategies emphasize progressive lightening after rewarming to normothermia to enable early neurological assessment and prognostication [45, 47]. The variability in sedation practices across institutions underscores the need for high-quality, methodologically rigorous trials to standardize best practices and optimize patient outcomes.

Sedation effects on the brain

Sedation has significant effects on cerebral physiology, with potential neuroprotective benefits, particularly in patients with acute brain injury [101, 130, 131]. By reducing the cerebral metabolic rate of oxygen, sedation may improve tolerance to ischemia and balance oxygen supply and demand, particularly when

autoregulation is impaired. This leads to decreased cerebral blood flow and volume, effectively lowering ICP. Monitoring ICP is a critical component of managing acute brain injury, as it helps clinicians adjust sedation depth to prevent ICP spikes triggered by arousal, agitation, pain, or sympathetic responses. Sustained elevated ICP is strongly associated with poor neurological outcomes, including increased mortality and long-term cognitive dysfunction [132-134].

Sedation may also enhance brain protection by promoting glymphatic system function, particularly when inducing non-REM sleep [135-137]. The glymphatic system facilitates the clearance of neurotoxic byproducts such as β-amyloid and tau-protein, potentially reducing the risk of neurodegeneration. This novel mechanism underscores the multifaceted role of sedation in supporting neuroprotection beyond its traditional focus on ICP management [138, 139].

Seizure management is another important consideration in sedation strategies for patients with acute brain injury and PCAS. Seizures, particularly status epilepticus and refractory status epilepticus, significantly increase cerebral metabolic demands and subsequently ICP, exacerbating secondary brain injury [89]. Sedatives such as propofol, barbiturates, and midazolam have anti-epileptic properties, enabling effective seizure control through increased sedation [140, 141]. Depending on the dosing, these drugs will suppress clinical myoclonus and epileptiform activity in the EEG. In refractory cases, high doses of sedatives may induce burst suppression on EEG, reducing metabolic demands and controlling seizures to prevent further injury. Current guidelines recommend continuous EEG monitoring within 24–48 hours for patients with acute brain injury or PCAS who are at risk of seizures, especially those who are comatose or sedated [47, 142]. However, there remains uncertainty whether deep sedation prophylactically reduces seizure risk and secondary brain injury, highlighting the need for further research to determine whether lighter sedation strategies is feasible in these patients without increasing the risk of seizure.

Hemodynamic stability is another crucial component of sedation management, as cerebral perfusion pressure, critical for oxygen delivery to the injured brain, is dependent on both MAP and ICP [128]. Sedation can influence blood pressure, heart rate, and systemic vascular resistance, often necessitating the use of vasopressors to maintain adequate MAP. In patients with impaired cerebral autoregulation, fluctuations in blood pressure can lead to inadequate cerebral perfusion or hyperperfusion and subsequent elevated ICP, with potential adverse effects on outcomes [78]. Thus, sedation strategies must balance neuroprotection with the prevention of hemodynamic instability to optimize care in acute brain-injured patients.

It is recommended that in comatose cardiac arrest survivors with clinical indicators of cerebral edema and elevated ICP, consideration may be given to invasive ICP monitoring [47]. However, while invasive ICP monitoring is standard in

neurocritical care for conditions like TBI, its routine use in post-cardiac arrest patients is not universally established. The decision to implement invasive ICP monitoring should be individualized, taking into account the patient's overall condition, the presence of signs indicating elevated ICP, and the expertise available within the treating facility.

Post-cardiac arrest patients face unique challenges related to hemodynamic instability, often resulting from factors such as cardiogenic shock and systemic inflammation associated with post-cardiac arrest syndrome [143]. Hypotension is particularly detrimental in this population, as it is strongly associated with unfavorable outcomes [68-76]. While it is possible to maintain adequate MAP during deep sedation in post-cardiac arrest care, meta-analyses of RCTs targeting higher or lower blood pressure levels have not demonstrated significant differences in mortality or functional outcomes [77, 78]. This suggests that blood pressure management during sedation must be individualized, balancing the risks of hypotension with the need for adequate cerebral perfusion.

Sedative drugs

The choice of sedative and analgesic agents in critically ill patients with acute brain injury and post-cardiac arrest syndrome is guided by their effects on cerebral physiology, hemodynamic, and the ability to facilitate frequent neurological assessments. Each agent has benefits and limitations, requiring careful selection to balance neuroprotection, hemodynamic stability, clinical seizures, and clinical neurological assessment.

Propofol is a widely favored sedative due to its rapid onset and short half-life, which allow for precise titration and timely neurological evaluation. It effectively reduces the cerebral metabolic rate of oxygen and lowers ICP while preserving cerebrovascular reactivity [144]. Additionally, propofol suppresses EEG activity in a dose-dependent manner, making it particularly effective as an anti-epileptic agent. Despite these benefits, propofol carries risks, including hypotension and propofol-related infusion syndrome, which necessitate cautious use and close hemodynamic monitoring [145, 146].

Midazolam, a short-acting benzodiazepine, has a more favorable hemodynamic profile compared to propofol but is slightly less effective in reducing cerebral blood flow and ICP [124]. Midazolam possesses strong anti-epileptic properties and is considered the first-line treatment for status epilepticus worldwide [147]. It is primarily metabolized in the liver, to metabolites with retained pharmacological activity, and are renally execrated. However, its active metabolites can accumulate, particularly in patients with renal impairment, leading to prolonged sedation, delayed awakening, and extended ICU stays [148]. Prolonged midazolam use has

also been associated with increased risks of delirium, post-traumatic stress disorder, and confounded neurological assessments [148].

Barbiturates also effectively reduce cerebral metabolic rate of oxygen and ICP but are associated with significant adverse effects, including prolonged sedation, increased risk of delirium, hemodynamic instability due to reduced cardiac contractility, electrolyte disturbances, and suppression of innate immunity. Currently, barbiturates are reserved for the management of refractory intracranial hypertension and status epilepticus, where their ability to induce burst suppression on EEG is critical for reducing cerebral metabolic demands and achieving seizure control [149, 150].

Dexmedetomidine, an alpha-2 adrenergic receptor agonist, provides titratable sedative and analgesic effects with minimal respiratory depression, making it particularly advantageous for critically ill patients. Its use has been associated with reduced risks of delirium, shorter durations of mechanical ventilation, and reduced ICU stays [151, 152]. Although its effects on cerebral physiology remain unclear, emerging evidence suggests potential neuroprotective properties, and studies have demonstrated its safety and efficacy in neurocritical care patients [153-155]. Nevertheless, dexmedetomidine may cause bradycardia and hypotension, necessitating careful hemodynamic monitoring in patients with acute brain injury [151, 152].

Ketamine, an N-methyl-D-aspartate receptor antagonist, is a short-acting sedative and analgesic agent with minimal impact on respiratory function and cardiovascular stability. Its role in cerebral physiology remains debated, but recent studies suggest that ketamine can stabilize or even reduce ICP while increasing cerebral blood flow [156, 157]. These findings indicate its potential utility in patients with acute brain injury, although further research is warranted to clarify its effects and safety in this context.

Analgesics

Opioids remain central to the management of analgesia in critically ill patients, particularly those with endotracheal tubes, as they effectively reduce discomfort and ventilator asynchrony. In recent years, clinical practice has shifted from long-acting opioids such as morphine to short-acting agents like, sufentanil, and remifentanil, which offer rapid onset and shorter half-lives, facilitating frequent neurological assessments. Morphine's metabolism in the liver and renal excretion can lead to metabolite accumulation in cases of renal or hepatic impairment, increasing the risk of neurotoxicity, including seizures and myoclonus. In contrast, fentanyl and sufentanil are less affected by such impairments, while remifentanil, metabolized via non-specific tissue and plasma esterase, offers an ideal pharmacokinetic profile for patients with compromised liver or kidney function. However, bolus opioid

dosing can decrease MAP and cerebral perfusion pressure, necessitating hemodynamic monitoring [158, 159]. For patients with acute brain injury and post-cardiac arrest syndrome, opioid selection and administration require careful consideration to balance analgesia with hemodynamic stability and timely neurological evaluations. While short-acting agents are preferred for their favorable pharmacokinetics, long-acting opioids may still have a role in specific clinical scenarios where prolonged analgesia is necessary.

Volatile anesthetics

The use of volatile anesthetics for sedation in critically ill patients is gaining interest as an alternative to intravenous sedation. Traditionally used in the operating room, agents such as sevoflurane and isoflurane are now being explored in the ICU due to their rapid onset, easy titration, and pulmonary elimination. Unlike intravenous sedatives, which rely on hepatic metabolism and renal clearance, volatile anesthetics are primarily eliminated via pulmonary exhalation, making them less susceptible to altered drug metabolism in critically ill patients, particularly those undergoing TTM or suffering from organ dysfunction. Volatile anesthetics can be challenging to use in the ICU because they are administered as gases, requiring specialized delivery systems and scavenging equipment not routinely available outside the operating room.

Among the commonly used volatile anesthetics, sevoflurane has low solubility, allowing for rapid induction and arousal from sedation, which is beneficial in ICU sedation when fast awakening is required. It is well tolerated in mechanically ventilated patients due to its minimal airway irritation, though it causes dose-dependent vasodilation and hypotension. Isoflurane, with a higher blood-gas solubility, has a slower onset but remains a potent cerebral vasodilator, which may increase ICP in patients with acute brain injury necessitating careful monitoring [160-162]. Volatile anesthetics may provide neuroprotective effects by reducing cerebral metabolic rate while maintaining cerebral blood flow and modulating neuroinflammation [162-164]. Studies suggest they may attenuate ischemia-reperfusion injury, oxidative stress, and excitotoxicity, potentially reducing secondary brain injury after TBI, stroke, or cardiac arrest. While volatile anesthetics present a promising alternative for ICU sedation, particularly in patients with acute brain injury and post-cardiac arrest syndrome, their clinical role remains to be investigated [165].

Pharmacokinetic challenges in critical illness

The metabolism and clearance of sedative drugs are significantly altered in critically ill patients, particularly in the setting of TTM and acute brain injury. Critical illness and hypothermia impair drug metabolism by reducing hepatic blood flow and

altering cytochrome P450 enzyme activity, resulting in slower and more variable drug elimination compared to healthy individuals [166, 167]. This delayed clearance increases the risk of drug accumulation and prolonged sedative effects, complicating the management of sedation and neurological assessments. Thus, the challenge of predicting drug pharmacokinetics in critically ill populations, particularly when hypothermia further impairs drug metabolism.

An additional consideration in ICU sedation infusions is the context-sensitive half-time, which refers to the time required for a drug's plasma concentration to decrease by half after stopping a continuous infusion. Unlike elimination half-life, which is a fixed property of a drug, context-sensitive half-time increases with prolonged infusions, particularly for lipophilic sedatives such as propofol and midazolam. In critically ill patients, prolonged sedation, reduced hepatic clearance, and impaired drug redistribution further prolong drug elimination, increasing the risk of delayed awakening and lingering sedation.

In the setting of TTM, hypothermia further prolongs context-sensitive half-time by reducing hepatic enzyme activity and renal clearance, making dose adjustments and careful titration essential to prevent excessive sedation and delayed neurological recovery [168-171]. Given these challenges, short-acting sedatives such as dexmedetomidine or remifentanil are often preferred in patients requiring prolonged sedation, as they have shorter context-sensitive half-times and more predictable clearance, even in the setting of critical illness and temperature modulation.

Heterogeneity in post-cardiac arrest patients

One critical aspect of post-cardiac arrest care that warrants further discussion is the significant heterogeneity among patients in terms of myocardial injury, brain injury, seizure susceptibility, and sedation/analgesia response. Patients are not a uniform group, and their physiological differences—including underlying comorbidities, the severity of ischemic injury, and individual pharmacokinetic variability—may lead to differing responses to the same treatment strategies. Evidence suggests that factors such as myocardial dysfunction, cerebral autoregulation impairment, and variations in seizure threshold contribute to variations in clinical outcomes, making a one-size-fits-all approach to sedation and analgesia potentially suboptimal [172-174].

Awakening

Neurological recovery following cardiac arrest follows a well-defined trajectory, extensively documented in prospective studies [175, 176]. The process typically begins with the restoration of brainstem function, marked by the return of spontaneous breathing and cranial nerve reflexes. This is followed by the

appearance of motor responses, including extension patterns and defensive movements. Consciousness gradually returns, accompanied by the progressive recovery of speech, motor functions, orientation, and memory.

While most patients regain consciousness within the first three days after cardiac arrest, delayed awakening has been observed in some cases, sometimes occurring weeks later [177]. Studies have reported that nearly 25% of patients awaken more than 72 hours after rewarming, with the latest documented case of awakening occurring 59 days post-rewarming in the absence of WLST [177]. However, beyond the timing of awakening, it is essential to consider the long-term quality of life in these patients. Earlier awakening has been associated with better functional outcomes, whereas delayed or absent awakening correlates with poorer neurological recovery and overall prognosis [178-180].

The awakening process may also be influenced by the use of sedative agents, which are often required during post-cardiac arrest care, can prolong time to awakening due to lingering effects. Both critical illness and hypothermia further contribute to delayed drug metabolism and reduced elimination, potentially leading to extended sedation and delayed neurological recovery. Recognizing the impact of residual sedation is crucial to ensuring accurate neurological assessments and avoiding premature prognostic conclusions.

Neurological prognostication

Brain injury remains the leading cause of death in patients who survive the initial phase of cardiac arrest. However, only a minority of these fatalities meet the formal criteria for brain death [181]. Instead, the majority of deaths result from the WLST following a predicted poor neurological outcome. Accurate neurological prognostication in unconscious patients following cardiac arrest is essential to guide clinical decision-making and avoid both premature WLST and futile care. To ensure prognostic accuracy, predictive tests must have a high specificity for poor neurological recovery. The 2021 European Society of Intensive Care Medicine and European Resuscitation Council algorithm suggests poor prognosis in patients with stereotyped flexion responses at 72 hours post-arrest if at least two predictors are present, including absent pupillary and corneal reflexes, bilaterally absent N20 somatosensory evoked potentials, malignant EEG patterns, elevated neuron-specific enolase, myoclonic status, or extensive anoxic brain injury on imaging [45]. However, the reliability of these predictors is influenced by residual sedation, metabolic disturbances, and other critical care-related confounders, necessitating careful interpretation.

To enhance the reliability of prognostication, a multimodal approach is recommended, incorporating clinical examination, neurophysiological testing, neuroimaging, and serum biomarkers of brain injury. However, many studies on

neurological prognostic markers are subject to self-fulfilling prophecy bias, which arises when treating clinicians, unblinded to predictive test results, allow these findings to influence WLST decisions [182]. Additionally, TTM complicates neurological prognostication, as sedative agents can interfere with both clinical assessments and neurophysiological tests, further obscuring accurate outcome prediction. Guidelines recommend a washout period of at least five context-sensitive half-lives of the longest-acting sedative before prognosis is determined [45].

Outcomes

Incorporating patient-centered outcomes is essential for a comprehensive evaluation of recovery after cardiac arrest. These outcomes focus on quality of life, functional independence, and the ability to return to normal activities, which are crucial for assessing the true impact of the event on survivors.

Survival

Survival is a robust outcome measure in cardiac arrest studies, indicating recovery objectively. However, its interpretation is influenced by the practice of WLST, and the specific time point recorded. Survival to discharge and 30-day survival are preferred over shorter-term metrics, yet both have limitations: survival to discharge varies by cultural and health system differences, while 30-day survival, though less biased, leading to higher follow-up loss. However, there is international variation in the feasibility of collecting this information. While multiple follow-up time points may be used to capture the trajectory of recovery, a 6-month follow-up is considered a strong endpoint, providing sufficient time for meaningful neurological and functional recovery while limiting the risk of unrelated events confounding outcomes.

Functional recovery

Neurological recovery continues for at least six months post-arrest, with the most significant improvements occurring within the first three months. Functional outcomes following cardiac arrest are typically assessed using clinician-completed measures, including the Cerebral Performance Category (CPC), Structured CPC, CPC-Extended, Glasgow Outcome Scale–Extended (GOSE), and the Modified Rankin Scale (mRS) [183-185].

The CPC scale, while widely used, has limited granularity, making it less favorable due to its inability to discriminate between different levels of recovery and a tendency to overestimate function [186]. In contrast, the mRS and GOSE provide

greater precision, with the mRS being more extensively used in cardiac arrest survivors.

The mRS is a brief, clinician-completed, ordinal scale that assesses functional limitations by focusing on restrictions in daily activities and social roles. While it effectively differentiates between mild and moderate disability, it does not capture specific residual impairments or distinguish whether disability results from neurological or non-neurological causes [187]. Recognizing its advantages, the International Liaison Committee on Resuscitation recommended in 2018 that the mRS be used for measuring functional recovery after cardiac arrest, citing its better discrimination between mild and moderate disability and its substantial interrater reliability [183]. However, despite this recommendation, many studies still rely on the CPC scale.

For clarity and statistical purposes, studies often dichotomize outcomes as 'good' or 'poor', though there is no universal consensus on what constitutes a poor neurological outcome. A systematic review found that 96% of studies on neurological prognostication after cardiac arrest define poor outcomes as CPC 3–5, while only 4% use CPC 4–5 [188]. When using the mRS, outcomes are commonly dichotomized into binary categories to facilitate interpretation and analysis. A common approach, derived largely from stroke trials, defines mRS 0–2 as a good outcome (indicating functional independence) and mRS 3–6 as a poor outcome. However, in the context of cardiac arrest, many studies have adopted a broader definition, classifying mRS 0–3 as a good outcome to reflect the realistic recovery trajectory in this population, where moderate disability may still represent a meaningful and acceptable quality of life [189]. This approach aligns with functional and clinical relevance while reducing the risk of underestimating the benefits of interventions in more severely affected patients.

For a detailed comparison of the CPC and mRS scoring systems, see Table 4.

Table 4.

Cerebral performance cathegory (CPC)		
CPC 1	Normal (good cerebral performance)	Conscious, alert, able to work and lead a normal life. May have minor psychologic or neurologic deficits
CPC 2	Moderate disability (disabled but independent)	Conscious, with sufficient cerebral function for part-time work in sheltered environment and independent activities of daily life. May have hemiplegia, seizures, ataxia, dysarthria, dysphasia, or permanent memory or mental changes
CPC 3	Severe disability (conscious but disabled and dependent)	Conscious, but dependent on others for daily support; has at least limited cognition. This category includes a wide range of neurologic dysfunction, from patients who are ambulatory but have severe memory disturbances or dementia that precludes independent existence to those who are paralyzed and can communicate only with their eyes (as in the locked-in syndrome).
CPC 4	Unconscious (coma or vegetative state)	Unconscious, unaware of surroundings, no cognition; no verbal or psychologic interaction with environment
CPC 5	Brain death	Meeting criteria for brain death or dead by traditional criteria
Modified Rankin Scale (mRS)		
mRS 0	No symptoms at all	
mRS 1	No significant disability despite symptoms	Able to carry out all usual duties and activities
mRS 2	Slight disability	Unable to carry out all previous activities, but able to look after own affairs without assistance
mRS 3	Moderate disability	Requiring some help, but able to walk without assistance
mRS 4	Moderately severe disability	Unable to walk and attend to bodily needs without assistance
mRS 5	Severe disability	Bedridden, incontinent and requiring constant nursing care and attention
mRS 6	Dead	

Aims of the thesis

The overall aim of the thesis

To evaluate the sedation and analgesia management during intensive care in patients resuscitated from out of hospital cardiac arrest and investigate the effect on outcomes.

The main aims of each paper are:

Paper I. To evaluate differences in patient-level sedation and analgesia dosing in an international multicenter trial to characterize current practice, differences between and within centers, and its effect on time to awakening, clinical seizures, and survival.

Paper II. To evaluate the sedation and analgesia management in post cardiac arrest care in an international multicenter trial, and its effects on time to awakening, clinical seizures, functional outcome, and survival.

Paper III. To determine the association of hypothermia versus normothermia after out of hospital cardiac arrest with administered cumulative doses of sedatives and analgesic drugs, serum concentrations of these drugs, and the effect on time to awakening.

Paper IV. To investigate the effects of different levels of sedation in critically ill adults with all-cause mortality and neurological outcome and serious adverse events.

Paper V. To design a protocol for a large clinical trial evaluating the effects of continuous deep sedation compared to minimal sedation on patient important outcomes in resuscitated out-of-hospital cardiac arrest patients.

Material and methods

Overview of the methods

Paper	I	II	III	IV	V
Study design	Post hoc analysis of a multicenter randomized clinical trial (TTM-trial)	Post hoc analysis of a multicenter, randomized trial (TTM2-trial)	Multicenter prospective substudy of the randomized clinical trial (TTM2-trial)	Systematic review and meta-analyses and trial sequential analysis	Protocol for the multifactorial randomized clinical trial; SED-CARE
Study sample	614 patients	1861 patients	71 patients	4352 patients	Sample size calculated to 3500 patients
Study period	2010-2013	2017-2020	2018-2020	Until June 2024	2024-ongoing
Method	Sedation and analgesia dosing at 12, 24, and 48 hours in unconscious adult OHCA patients with presumed cardiac cause	Sedation and analgesia dosing at 72 hours in unconscious adult OHCA patients	Serum concentrations and dosing of sedation and analgesia at 40 and 72 hours in unconscious adult OHCA patients	Randomized clinical trials investigating sedation depth in critically ill adults	
Data analyses	Analysis of variance. Multivariate hierarchical linear regression model. R-squared and likelihood ratio testing.	Chi-square analyses. Multiple logistic regression model.	Kaplan-Meier estimate and log rank test. Multiple linear regression model.	Meta-analyses and trial sequential analyses	
Ethical approval	Ethical approval by Regional Ethical Review Board Lund, Protocol 2009/6 Dnr 2009/324	Ethical approval by Lund University in 2015 (Dnr 2015/228)	Ethical approval by Lund University in 2015 and 2017 (Dnr 2015/228 and 2017/36)	N/A	Ethical approval by Swedish Ethical Review Authority (Dnr 2022-02425-01) and (Dnr 2023-00198-02)

Paper I

Study design and overview of the TTM-trial

This study is a post-hoc analysis based on the TTM-trial, an international, multicenter, randomized, parallel-group study conducted from 2010 to 2013. The TTM-trial aimed to compare survival and neurological outcomes at six months in comatose survivors of OHCA randomized to TTM at either 33°C or 36°C. A total of 950 adult patients were randomized to either group, with modified intention-to-treat groups comprising 473 patients at 33°C and 476 at 36°C.

This post-hoc analysis focuses on sedation and analgesia practices during TTM and their potential associations with clinically relevant outcomes. This study retrospectively examines sedation and analgesia dosing, its variability across centers, and its impact on awakening, seizure occurrence, and six-month survival.

Randomization and ethical considerations

The TTM-trial utilized a 1:1 randomization strategy, stratified by center and conducted via a web-based application. Participating centers were required to be high-volume ICUs with treatment capabilities, including percutaneous coronary intervention and standardized TTM protocols. Ethical approval was obtained from local ethics boards in all participating countries and the Regional Ethical Review Board at Lund University. Surviving patients provided informed consent, while next of kin were informed about study inclusion during initial hospital contact. Additionally, interim analyses were conducted by the data safety monitoring board to ensure participant safety.

Participants

The TTM-trial included adults aged 18 years or older who remained unconscious (Glasgow Coma Scale (GCS) <8) after OHCA with sustained ROSC. Exclusion criteria included unwitnessed asystole as the primary rhythm, presumed non-cardiac causes of arrest, ROSC-to-screening time >240 minutes, and refractory hypotension. Other exclusions included pregnancy, bleeding disorders, acute strokes, and pre-arrest limitations in care. For this post-hoc analysis, patients were further excluded if sedation data were missing or if fewer than 10 patients from a center had complete sedation data.

Sedation and analgesia practices

Sedation was mandatory during the 36-hour intervention period, with sedation and analgesia management left at the discretion of the physician and individual centers, which allowed to reflect real-world practice. Sedative drug doses and monitoring practices were retrospectively collected via online questionnaires distributed to trial sites in 2015–2016. Cumulative doses of sedatives and analgesics were reported at 12, 24, and 48 hours and converted to midazolam and fentanyl equivalents to enable comparisons. These timepoints were chosen for practical reasons, as intensive care units typically document data every 12 hours. The use of equivalents allowed for the standardization of dosing practices across different centers and agents.

Neurological management and outcome definitions

Awakening was defined as achieving a GCS motor score of 6, indicative of command obedience, and was assessed daily in the ICU. Seizures were recorded daily, categorized as myoclonic or tonic-clonic, and assessed for duration (less or more than 30 minutes). The TTM-trial applied strict criteria for WLST, ensuring standardized care.

Outcomes

The outcomes for this post-hoc analysis was:

- Time to awakening: Early (days 1–4) versus late (day 5 or later) awakening.
- Clinical seizures: Defined as myoclonic or tonic-clonic seizures occurring during the ICU stay.
- Survival at six months: Assessed as part of the original TTM-trial's follow-up, with outcome assessors blinded to the allocation group for the survival outcome.

Statistical analyses

Cumulative sedative and analgesic doses were collected for each patient at 12, 24, and 48 hours and converted to midazolam- and fentanyl- equivalents and averaged over weight (kilogram) and time (hours). These doses were analyzed for variability in administration patterns, including number of sedatives and analgesics, dose, and titration between timepoints, across centers. Variables included in the multivariate models were selected based on their potential impact on the administration of sedatives and analgesics, aiming to account for factors that might influence dosing decisions and clinical context. Multivariate models were created to assess

associations between sedation and analgesia practices and clinical outcomes, adjusting for baseline patient and cardiac arrest characteristics such as age, sex, shockable rhythm, and time to ROSC.

Hierarchical logistic regression was employed to explore center-level variability and its influence on outcomes. These models compared sedation and analgesia dosing, titration patterns, and clinical outcomes. Additionally, center-specific effects were evaluated using likelihood ratio testing and R-squared values to identify the extent to which institutional protocols influenced observed variability.

Hierarchical logistic regression

Hierarchical logistic regression was used to explore center-level variability and its influence on outcomes. Unlike standard logistic regression, hierarchical logistic regression incorporates a multi-level structure in the data, allowing for the inclusion of nested variables. In this study, patients are nested within centers, and the model accounts for this clustering to better capture the influence of center-specific practices. This approach is particularly beneficial in multi-center studies, where center-level effects, such as institutional protocols, staffing, and resource availability, may systematically affect outcomes. By including random effects for centers, hierarchical models estimate variability at both the patient and center levels, providing more nuanced insights compared to traditional logistic regression, which assumes independence of observations.

Likelihood ratio testing

Likelihood ratio testing was used to evaluate the significance of center-specific effects in the models. This statistical test compares the goodness-of-fit between two nested models: one with and one without the center-level random effects. A significant likelihood ratio test indicates that the inclusion of center-specific random effects improves model fit, suggesting that institutional variability plays a significant role in sedation and analgesia practices on outcomes. This method is particularly valuable in determining whether center-level differences warrant further investigation or whether they can be disregarded.

R-squared values

R^2 values were employed to quantify the proportion of variance in outcomes explained by the models, providing a measure of model performance. In hierarchical models, different forms of R^2 values, such as marginal (accounting for fixed effects only) and conditional (accounting for both fixed and random effects), were used to assess the contribution of center-specific factors. Comparing these values allows for an understanding of how much variability is attributable to the center effect.

The TTM2-trial: Paper II and III

The TTM2-trial was a large, international, multicenter, investigator-initiated, open-label randomized clinical trial designed to compare the effects of two temperature management strategies, targeted hypothermia (33°C) and targeted normothermia (<37.8°C), on survival and neurological outcomes in unconscious patients after OHCA. Conducted between November 2017 and January 2020, the trial enrolled 1900 adult patients across 61 sites in 14 countries.

Patients

The inclusion criteria were chosen to maximize clinical relevance and applicability while focusing on patients likely to benefit from TTM. Eligible patients were unconscious adults (>18 years) who achieved sustained ROSC after OHCA and were eligible for intensive care. The randomization window was 180 min after ROSC. The exclusion criteria, such as unwitnessed arrests with asystole, were implemented to avoid confounding such as conditions with extremely poor prognoses. Other exclusion criteria include admission temperature below 30°C pre-ROSC, ECMO, pregnancy, intracranial bleeding, and severe chronic obstructive pulmonary disease requiring home oxygen therapy.

Ethics

The TTM2-trial was conducted in compliance with the Declaration of Helsinki and approved by the relevant ethics committees in each participating country. Written informed consent was obtained from a legal surrogate or deferred in accordance with local regulations until the patient regained mental capacity. The trial included two prespecified blinded interim analyses by an independent data and safety monitoring board and was monitored according to GCP. The study protocol was registered at ClinicalTrials.gov (NCT02908308) and was monitored by an independent data and safety monitoring committee.

Patient management

Intervention and post-intervention periods

Participants were randomized 1:1 to targeted hypothermia (33°C) or targeted normothermia (<37.8°C). In the hypothermia arm, cooling was initiated immediately using surface or intravascular devices and maintained for 28 hours,

followed by controlled rewarming to 37°C over 12 hours. In the normothermia group, fever (>37.8°C) was managed with cooling devices and the target was to keep the temperature below 37.5°C. If the temperature reached 37.8°C, cooling was initiated to maintain 37.5°C. These approaches allowed for a pragmatic comparison of active cooling versus fever prevention, with mechanical ventilation and deep sedation targeted in both groups to control discomfort and minimize variability between groups.

In both intervention groups, extubation was attempted as soon as possible based on standard ICU protocols. For participants who remained comatose or sedated at 40 hours after randomization, temperature was maintained within the normal range to avoid fever (>37.8°C) until 72 hours post-randomization. Use of temperature management devices during this period was at the discretion of the treating physician. Neurological evaluation was performed after at least 96 hours by a physician blinded to group allocation.

Beyond temperature management and WLST criteria, the TTM2-trial protocol did not mandate specific monitoring or therapy beyond standard care. Instead, general ICU management followed international and local guidelines to reflect real-world clinical practices. This pragmatic approach balanced trial protocolization with flexibility to account for varying local practices.

Neurological prognostication and WLST

A strict protocol for neurological prognostication was integral to the TTM2-trial to mitigate potential bias due to the open-label nature of the study. Prognostication was mandatory for all participants remaining in the ICU at 96 hours post-randomization, aligning with European Resuscitation Council and European Society for Intensive Care Medicine recommendations [45]. A neurologist, intensivist, or other experienced specialist, blinded to group allocation, conducted the prognostication to determine if a patient met the criteria for a likely poor neurological outcome. This result was recorded and communicated to the treating physician. Decisions regarding WLST were made by treating physicians in consultation with relatives or legal surrogates, as required by local legislation. For participants undergoing neurological prognostication, data were collected on when sedation was discontinued.

General intensive care

General ICU care was planned to be consistent across both trial groups according to local standardized care plans, managed by treating physicians. Key elements included fluid therapy, hemodynamic support, respiratory management, metabolic disturbance correction, and seizure management, all following local protocols.

Cardiac interventions were guided by local protocols, ensuring around-the-clock invasive management availability.

Sedation

Sedation was mandatory during the 40-hour intervention period to ensure patient comfort, control shivering, and standardize conditions for both groups. Deep sedation (RASS -4/-5) was targeted, and while a specific sedation protocol was not mandated, the use of short-acting drugs or volatile anesthetics was recommended. This minimized differences in sedation management between the hypothermia and normothermia groups, reducing potential confounding and ensuring that the groups were managed equivalently to better isolate the effects of the intervention. Beyond 40 hours, sedation was tapered or discontinued based on the patient's clinical state, as prolonged sedation was discouraged in line with international guidelines.

Cumulative dosing of sedatives and analgesics up to 72 hours post-randomization was prospectively recorded, including midazolam, propofol, dexmedetomidine, clonidine, esketamine, ketamine, fentanyl, morphine, remifentanil, and oxycodone. Management of shivering was guided by the Bedside Shivering Assessment Scale (BSAS) (See Table 5), with treatments such as acetaminophen or local standard regimens. If necessary, sedation was increased, or neuromuscular blockade (NMB) agents were administered to maintain a BSAS score of 0–1.

Table 5. Bedside Shivering Assessment Scale.

Bedside Shivering Assessment Scale (BSAS)		
BSAS	Classification	Description
0	None	No shivering
1	Mild	Shivering localized to neck/thorax, may be seen only as artifact on ECG or felt by palpation
2	Moderate	Intermittent involvement of the upper extremities +/- thorax
3	Severe	Generalized shivering or sustained upper/lower extremity shivering

Outcomes and follow-up

The primary outcome of the TTM2-trial was six-month mortality. Secondary outcomes included poor functional outcome (mRS 4–6) at six and 24 months. Follow-up assessments began 30 days after cardiac arrest, conducted either face-to-face or via telephone using the mRS scale. Follow-ups at six and 24 months involved clinic visits, where trained and blinded assessors evaluated cognitive function, quality of life, return to work, and cardiovascular risk factors. Assessors underwent rigorous training and adhered to detailed protocol to ensure consistency and accuracy.

Paper II

Objectives

This study aimed to evaluate the sedation and analgesia management in post cardiac arrest care in an international multicenter trial. Additionally, this study aimed to investigate the effect of sedatives and analgesics on outcomes and analyzed clinical factors and severity of illness factors influencing the sedation administration. We hypothesize that there is an association between higher doses of sedatives and analgesics and long-term good functional outcome and survival, and occurrence of clinical seizures, and late awakening.

Study design and population

Paper II was a post hoc analysis of the TTM2-trial, designed to explore associations between sedation and analgesia practices during post-cardiac arrest care and their impact on clinical outcomes, including survival, neurological function, clinical seizures, and late awakening. The analysis included data from 1861 patients from 61 centers across 14 countries enrolled in the TTM2-trial. This broad cohort ensured a high degree of generalizability while reflecting real-world variability in sedation practices across international centers.

The decision to perform a post hoc analysis allowed for a focused investigation into how sedation and analgesia practices influenced outcomes within the structured framework of the TTM2-trial. While the observational nature of this analysis precluded causal inferences, the randomized design of the TTM2-trial mitigated some biases, such as confounding by treatment group allocation. This approach provided valuable insights into clinical practices and outcomes, despite not being primary endpoints of the TTM2-trial.

Subgroup analyses: Comatose patients at 96 hours without clinical seizures

Patients comatose at 96 hours without clinical seizures were included in this subgroup, as the comatose at 96 hours and thus subjects to neurological prognostication they are the population most likely to benefit from optimized sedation strategies. Patients with clinical seizures were excluded, as their presence could significantly impact sedation management and confound the analysis. For the patients who underwent neurological prognostication, the time of sedation discontinuation was recorded, allowing for calculation of the duration of sedation and the average dose of sedatives and analgesics as dose per kilogram per hour.

Data collection and outcome measures

Data on sedation and analgesia practices with total doses up to 72 hours, shivering management, and the use of NMB, and neurological prognostication were collected, according to the main TTM2-trial. Sedative doses were categorized into quartiles to facilitate dose-response analyses, and their associations with outcomes were explored using multivariable regression models. Potential confounders, including age, sex, baseline neurological status, severity markers, and clinical events such as clinical seizures were adjusted for in the multivariable regression model.

The primary outcomes analyzed in were survival and good neurological function at six months, defined as a modified Rankin Scale (mRS) score of 0–3. Secondary outcomes included time to awakening, the occurrence of clinical seizures. Subgroup analyses were performed similarly to investigate the role of sedation in patients without clinical seizures who remained comatose at 96 hours.

Statistical analyses

Cumulative doses of sedatives and analgesics were adjusted for body weight and expressed as milligrams (mg) or micrograms (mcg) per kilogram, as appropriate. Continuous variables were summarized as medians with interquartile ranges (IQR) or means with standard deviations (SD), while categorical variables were reported as percentages. To explore dose-response relationships for propofol, doses were categorized into quartiles due to observed non-linearity, whereas the administration of midazolam, fentanyl, and remifentanil was treated as binary variables.

Propofol doses were analyzed using chi-square statistics applied to test associations with clinical outcomes, including good functional outcome (mRS 0–3) and survival at 6 months, as well as the occurrence of clinical seizures and late awakening. Additionally, the associations between propofol quartiles, midazolam, fentanyl, and remifentanil use and these outcomes were further assessed in multivariable logistic regression models. The models were adjusted for potential confounders, such as age, sex, witnessed arrest, shockable rhythm, time to ROSC, shock on admission, body mass index, TTM level, shivering, and the administration of NMB agents. Markers of illness severity, including lowest glomerular filtration rate and highest bilirubin levels, were also included to account for potential confounding factors influencing sedative administration. To compare sedative and analgesic doses in hypothermia versus normothermia groups, Wilcoxon rank-sum or Wilcoxon rank-sum exact tests were used for continuous variables, while Pearson’s chi-square test was applied for categorical variables.

Paper III

Objectives

Paper III focused on investigating the association between the two TTM strategies and the serum concentrations of sedatives and analgesics, as well as the time to awakening after OHCA.

Patients

This substudy included 71 patients who survived the initial 40-hour intervention period and were treated at three Swedish TTM2-trial centers. This selection minimized confounding from early mortality or deviations from the trial protocol but may limit the generalizability to patients with poorer prognoses.

Intervention and sedation management

Deep sedation was mandatory during the 40-hour intervention period. Short-acting agents, such as propofol and remifentanil, were recommended to facilitate rapid neurological assessments after the intervention. While this standardized approach ensured comparability within the three included centers, it may not reflect variability in sedation practices across centers or regions. Cumulative doses of sedative and analgesic drugs, including midazolam, propofol, dexmedetomidine, clonidine, esketamine, ketamine, fentanyl, morphine, remifentanil, and oxycodone, were recorded from 0–40 (end of intervention) and 40–72 (end of targeted normothermia) hours post-randomization.

Seizure management

Local protocol (3 sites: Malmö, Helsingborg, and Lund) stated that all epileptic seizures, whether clinical and/or electrographic, mandated treatment with an antiepileptic drug (AED). Hence, the time (day and hour) of initiated treatment with AED was registered and used as a marker of epileptic seizure activity in this study. The first choice of drug was valproic acid or levetiracetam, while second-line drugs included phenytoin, fosphenytoin, diazepam, clonazepam, lorazepam, topiramate, phenobarbital, or lacosamide at the discretion of the treating physician.

Serum sampling and analysis

Blood samples were collected at two critical time points: at the end of the intervention period (40 hours post-randomization) and at the end of fever prevention period (72 hours post-randomization). Samples were drawn into EDTA tubes to prevent coagulation and were promptly transported to the hospital's laboratory services. There, the samples were centrifuged to separate the serum and subsequently frozen at -20°C to preserve the stability of the analytes.

Analysis was performed at the Department of Forensic Chemistry, The National Board of Forensic Medicine, University of Linköping, Sweden. To ensure the integrity of the samples during transport to Linköping, Sweden, they were transported under temperature-controlled conditions. Analyses were conducted using liquid chromatography-tandem mass spectrometry and gas chromatography–mass spectrometry, a validated method specifically adapted for use in critically ill patients. This methodology allowed for precise quantification of sedatives and analgesics, including propofol, midazolam, clonidine, dexmedetomidine, morphine, and fentanyl, even at low concentrations. Remifentanil was excluded due to its rapid metabolism.

The liquid chromatography-tandem mass spectrometry technique was crucial for its high sensitivity and specificity, ensuring reliable measurements in a patient cohort with complex pharmacokinetics due to critical illness [190]. To further ensure reliability, sample analyses were batched and processed every four months, minimizing the risk of degradation, and ensuring consistency across the study period.

Outcomes

The primary outcomes, cumulative dosing, serum concentrations, and time to awakening, were chosen to link sedation strategies with clinical outcomes. Time to awakening was a particularly relevant outcome for evaluating neurological recovery, but this measure was influenced by patient-specific factors such as baseline brain injury and metabolic status. The time (day and hour) of sedation discontinuation and time to awakening were also documented. Consciousness was defined as Full outline of unresponsiveness (FOUR) score motor component of four (obeying commands).

Statistical analyses

Continuous data were summarized using the median and IQR to account for non-normal distributions, and comparisons between groups were conducted using the Wilcoxon rank-sum test or Wilcoxon rank rum exact test. Categorical variable

reported using percentages and significance was tested using Pearson's Chi-square test to evaluate differences in proportions. To examine the probability of awakening from sedation discontinuation up to 180 days post-randomization, Kaplan-Meier survival estimates were utilized, and the log-rank test was applied to compare survival distributions between groups. Sensitivity analyses were performed within subgroups of patients receiving midazolam and those without midazolam to assess the differential impact of long-acting versus short-acting sedatives, enhancing the robustness of the findings.

The association between propofol concentrations at 40 and 72 hours and TTM levels was evaluated using linear regression to identify potential effects. To control for confounding and account for illness severity, additional variables including age, sex, body mass index, peak neuron-specific enolase, peak bilirubin, and propofol dose at 40 and 72 hours were added to the models to adjust for severity of illness. The relationship between propofol dose and the occurrence of shivering or seizures was also explored using linear regression. Furthermore, differences in midazolam doses at 40 and 72 hours between patients with and without seizures were analyzed using the Wilcoxon rank-sum test. The application of these statistical methods ensures a comprehensive analysis while addressing potential biases and limitations related to non-normality, confounding factors, and the impact of sedative pharmacokinetics on patient outcomes.

Paper IV

Systematic review and meta-analysis

Systematic reviews and meta-analyses are essential tools in evidence-based medicine, providing a comprehensive synthesis of existing research. A systematic review involves a structured, transparent, and replicable process for identifying and synthesizing all relevant studies on a specific topic, ensuring methodological rigor, and minimizing bias. This replicable approach enhances reliability, allows for independent verification, and facilitates the consistent application of findings in clinical practice. By pooling data from multiple studies, these methodologies increase the statistical power to detect treatment effects and offer more precise estimates of intervention efficacy and safety. Thus, offer the potential to decrease the number of false-negative results and prevent delays in the introduction of effective interventions into clinical practice [191]. This approach helps address discrepancies between individual studies, providing a higher level of evidence and identifying trends and patterns that might not be evident in single studies. In the context of sedation in critically ill patients, a systematic review with meta-analysis can elucidate the comparative benefits and harms of different sedation strategies, thereby informing clinical guidelines and improving patient care.

Rationale for trial sequential analysis

Trial sequential analysis (TSA) is a statistical method used in cumulative meta-analyses to address random errors from repeated significance testing in accumulating data [192-194]. It applies principles from interim analyses in clinical trials, establishing futility and efficacy boundaries to indicate when sufficient evidence has been reached [195]. Futility boundaries show when further studies are unlikely to change conclusions, while efficacy boundaries confirm when evidence is robust enough to support an effect or if further research was warranted. TSA also calculates the required information size, similar to sample size calculations in single trials, to ensure adequate statistical power [193, 194]. By accounting for diversity among studies, TSA reduces the risks of type I (false positive) and type II (false negative) errors, making results more reliable [193, 194]. In the context of sedation strategies for critically ill or cardiac arrest patients, TSA helps determine when evidence is strong enough to guide clinical decisions, preventing unnecessary research and promoting timely, evidence-based care.

Methodological approach

Conducting a systematic review and meta-analysis requires adherence to a well-defined protocol and rigorous methodology to ensure transparency and objectivity [191]. For this study, a protocol was developed and followed, however not included in this thesis. The process begins with a comprehensive literature search using an extensive strategy across multiple databases and clinical trial registries to identify all relevant RCTs comparing varying degrees of sedation in critically ill adults. Pre-defined inclusion and exclusion criteria were applied to ensure consistency in study selection, and independent data extraction by multiple reviewers minimized errors and ensured accuracy.

Pooling treatment effects across trials is a critical step in meta-analysis, requiring careful exploration and management of heterogeneity arising from differences in study populations, interventions, and outcome measures [191]. This review acknowledged potential challenges, including statistical and clinical heterogeneity due to the diversity of sedative drugs and patient populations. Beyond addressing heterogeneity, the quality of included studies was critically assessed using the Cochrane Risk of Bias Tool 2 (Rob2), while the overall certainty of evidence was evaluated with the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach, providing a structured framework for evaluating evidence quality and strength of recommendations. These tools, internationally recognized for their rigor and ensure a systematic and transparent evaluation of the evidence.

Objectives

This systematic review with meta-analysis and TSA aimed to assess the current evidence on the effects of different levels of sedation on outcomes in critically ill adult patients to provide evidence of the optimal sedation strategies, evaluating the therapeutic benefits against potential adverse effects, to provide robust evidence for guiding clinical practice.

Data sources and search strategy

A systematic literature search was conducted across the following databases: CENTRAL, MEDLINE, Embase, LILACS, and Web of Science. The search covered all available records up to June 13, 2023. Specific search terms included “sedation OR hypnotics” AND “critically ill OR critical care OR intensive care” AND “adult” AND “meta-analyses”. Additional manual searches of reference lists of relevant articles and conference proceedings were performed to ensure a comprehensive inclusion of studies.

Inclusion and exclusion criteria

- RCTs involving critically ill adults (18 years of age or older) admitted to intensive care units.
- Studies comparing different levels of sedation (e.g., lighter versus deeper sedation or no sedation vs sedation).

Studies were not eligible if no separation of targeted sedation depth could be identified.

Data extraction and management

Data were independently extracted by two reviewers using a standardized extraction form. Discrepancies were resolved through discussion or consultation with a third reviewer. Extracted data included:

- Study characteristics (e.g., authors, publication year, study design).

- Participant characteristics (e.g., sample size, demographics).

- Intervention details (e.g., sedation levels, duration).

- Outcomes (e.g., mortality, adverse events).

Risk of bias assessment

The risk of bias for each included study was assessed using the Cochrane Rob2 to evaluate the potential for bias in the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias.

Data synthesis and analysis

Aggregate data were synthesized using meta-analysis techniques to estimate pooled effect sizes. Risk ratios (RR) with 95% confidence intervals (CI) were calculated for dichotomous outcomes. Both random- and fixed-effects model was reported and the model with the highest p-value were used to account for potential heterogeneity among studies.

Trial sequential analysis

TSA was employed to reduce the risk of random errors due to repetitive testing of accumulating data. TSA calculates the required information size (i.e., the sample

size needed to confirm or refute the anticipated intervention effect) and constructs monitoring boundaries to determine whether the cumulative evidence is sufficient and conclusive, while controlling for type I and type II errors.

Compared to other statistical methods, TSA has several advantages. Bayesian Meta-Analysis dynamically updates probability distributions based on prior knowledge, offering a flexible approach but introducing potential subjectivity due to reliance on prior distributions. Cumulative Meta-Analysis, which updates effect estimates as new studies are included, lacks control for repeated significance testing, increasing the likelihood of false positive results. The Sequential Probability Ratio Test is useful for making interim decisions in clinical trials but does not adjust for heterogeneity in meta-analyses, limiting its applicability to systematic reviews. Thus, TSA is superior these methods by adjusting for heterogeneity and multiple testing, enhancing the reliability of systematic reviews and meta-analyses.

Certainty of evidence

The GRADE approach was used to assess the certainty of evidence. This approach considers the risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Ethical considerations

As this study involved the synthesis of previously published data, ethical approval was not required. However, the study adhered to ethical principles in the conduct of research and reporting of results.

Registration

This systematic review and meta-analysis and TSA were registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42023386960).

Paper V

Study design

This study, the Sedation after Cardiac arrest and Resuscitation trial (SED-CARE) trial, is a robust randomized, international, multicenter, parallel-group trial designed to evaluate the effects of continuous deep sedation versus minimal sedation on clinical outcomes in patients who are comatose following OHCA. The SED-CARE trial is part of the larger Sedation, Temperature, and Pressure after Cardiac Arrest and Resuscitation trial (STEPCARE) factorial trial, which includes additional interventions related to blood pressure and temperature management. This design allows for simultaneous exploration of multiple critical interventions in post-cardiac arrest care, utilizing collective resources and facilitating the simultaneous evaluation of multiple intervention while maintaining the independence of each study arm.

The trial methodology adheres to established guidelines, including the *Standard Protocol Items: Recommendations for Interventional Trials* protocol for study design and *The Consolidated Standards of Reporting Trials* reporting standards for randomized clinical trials. These frameworks ensure a comprehensive, transparent, and replicable study process. By embedding SED-CARE within the broader STEPCARE trial, the study benefits from the collaboration and expertise of a diverse, international network of researchers and clinicians, further enhancing its relevance and generalizability.

Participants and inclusion criteria

The study includes adult patients (≥18 years) who suffer from OHCA and achieve sustained ROSC, defined as a period of at least 20 minutes during which spontaneous circulation is maintained without the need for chest compressions. Eligible patients must remain unconscious after ROSC, as indicated by an inability to obey verbal commands (FOUR motor score < 4) or require sedation due to agitation. Exclusion criteria are applied to avoid confounding factors and are trauma or hemorrhage as the presumed cause of arrest, pregnancy, suspected or confirmed intracranial hemorrhage, prior participation in the STEPCARE trial, or the use of ECMO before randomization.

The inclusion window for enrolment is intentionally narrow (4 hours after ROSC) to align with the critical early stages of post-resuscitation care, when interventions are most likely to influence outcomes. This timeframe balances the urgency of initiating interventions with the practicalities of patient screening and randomization.

Randomization and blinding

To maintain the scientific rigor of the trial, a web-based randomization platform ensures concealed allocation using stratified permuted blocks by trial site. Stratification by trial site accounts for potential variations in practice patterns across participating centers.

While blinding the clinical team responsible for patient care is impractical due to the nature of sedation interventions, extensive measures are in place to mitigate bias. For instance, outcome assessors, statisticians, and members of the steering committee are blinded to treatment allocation. This ensures that data interpretation and final analyses remain unbiased. Allocation codes are retained securely and will only be revealed after all analyses are complete, further maintaining the integrity of the study.

Interventions

The two intervention groups represent distinct strategies to post-resuscitation sedation management.

Continuous deep sedation group

Patients randomized to this group receive continuous intravenous infusion of short-acting sedatives, such as propofol, to achieve a RASS score of -4/-5. The clinical team assesses the sedation level according to RASS every fourth hour. This level corresponds to deep sedation, where patients are unresponsive to voice stimuli. Sedation is maintained for 36 hours after randomization, with adjustments made as needed to sustain the target depth. After the intervention period, sedation practices revert to the discretion of the treating physician.

Minimal sedation group

In this group, sedative use is minimized, with a target RASS score of 0 to -2. This approach prioritizes early reduction or discontinuation of sedatives, ideally within 6 hours of randomization. Pain management is emphasized to ensure patient comfort, employing multimodal strategies such as acetaminophen and opioids. Sedatives are reserved only for cases where clinical safety or comfort cannot be achieved otherwise. This strategy encourages earlier awakening, potentially allowing more accurate neurological prognostication and faster progression toward extubation and ICU discharge.

Outcome measures

The primary outcome of the trial is all-cause mortality at six months post-randomization. This outcome was selected for its objectivity and clinical relevance, as it captures the ultimate impact of the intervention on patient survival. The timing was chosen as it captures both early and longer-term survival outcomes, reflecting the intervention's impact beyond the acute phase of care. Six months is also a widely accepted timeframe in cardiac arrest research, providing sufficient time for neurological recovery and stabilization of outcomes, while avoiding confounding from other health or unrelated events that may emerge with longer follow-up periods. Moreover, it aligns with recommendations from core outcome sets like COSCA, ensuring comparability with other studies in the field.

Secondary outcomes provide a broader perspective on the intervention's effects and include:

- Functional outcomes assessed using the modified Rankin Scale (mRS), dichotomized into favorable (mRS 0-3) and poor (mRS 4-6) outcomes.
- Serious adverse events occurring during the ICU stay, such as sepsis, arrhythmias requiring intervention, venous thromboembolism, and significant bleeding.
- Patient-reported quality of life measured using the EQ-5D-5L visual analog scale at 6 months follow-up.

Exploratory analyses will assess ventilator- and hospital-free days and time-to-event outcomes.

These outcomes ensure a comprehensive evaluation, capturing not only survival but also the quality and functionality of that survival.

Sample size and statistical analysis

The trial's sample size of 3,500 participants reflects a rigorous calculation designed to detect an absolute risk reduction of 5.6% in six-month mortality. This corresponds to a clinically meaningful relative risk reduction of 9.3%. The calculation assumes 60% mortality in the control group, consistent with prior cardiac arrest trials, and incorporates allowances for potential loss to follow-up and minor factorial interactions.

Statistical analyses will follow an intention-to-treat approach, preserving the benefits of randomization and providing a real-world assessment of the intervention's effectiveness. We will analyze dichotomous outcomes using mixed effects generalized linear models using a log-link function with 'site' as a random intercept using an exchangeable covariance matrix, and we will include the allocated intervention in the two other trials as fixed effects. Continuous outcomes will be

assessed using mixed effects linear regression, similarly incorporating 'site' as a random intercept with an exchangeable covariance matrix and adjusting for the allocated interventions from the other trials. Sensitivity analyses will explore potential variations in treatment effects across key demographic and clinical variables.

Data collection and management

Detailed patient data will be collected through standardized electronic case report forms, ensuring consistency and accuracy across sites. Data points include sedation depth and medication dosages (every fourth hours during intervention and at 72 hours after randomization), physiological parameters, and clinical outcomes. To ensure data quality, site personnel receive training and support from the coordinating team, which oversees data management and monitors adherence to the protocol.

Ethical considerations

Given the urgency of the intervention, a delayed consent process is employed. Patients unable to provide informed consent upon enrolment will have consent obtained from their legal representatives. For patients who regain decision-making capacity, informed consent is sought retrospectively. Data from deceased participants will also be utilized and is included in the ethical approval, to ensure comprehensive analysis and avoid survival bias. The consent process will vary from site to site and will align with local ethical approvals, national laws, and the Declaration of Helsinki [196].

Monitoring and interim analysis

The Data and Safety Monitoring Committee (DSMC) plays a critical role in overseeing participant safety and trial integrity. Interim analyses are conducted after the first 500 participants have been included, assessing safety, efficacy, and potential interactions between trial interventions. The DSMC has the authority to recommend further interim analyses, modifications, or discontinuation of the trial based on predefined stopping criteria or emerging evidence from other studies.

Results

Detailed descriptions of the results are available in the separate papers (see attachments)

Paper I

Study population and participating centers

The study included 614 patients from 18 centers. Of these, 163 patients (26%) were treated in a cardiac ICU at a single center, while the remaining 451 patients (74%) were treated in mixed ICUs across the other 17 centers.

Assessment tools for sedation and analgesia

RASS was the primary tool used to assess sedation, implemented in 15 centers, and including 533 patients (87%). The Critical Care Pain Observation Tool was used in one center for 29 patients (4%).

Administration of sedatives and analgesics

Most patients (99%) received sedatives at all time points assessed (12-, 24-, and 48-hours after randomization). Analgesics were administered to 85% of patients at 12 hours, 86% at 24 hours, and 83% at 48 hours. Significant inter-center variability in the number of sedatives and analgesics administered was observed at all time points ($p < 0.01$, chi-square test), see Figure 2. These differences remained statistically significant after adjusting for age, sex, time to ROSC, bystander CPR, shockable rhythm, and shock on admission ($p < 0.001$).

Figure 2.

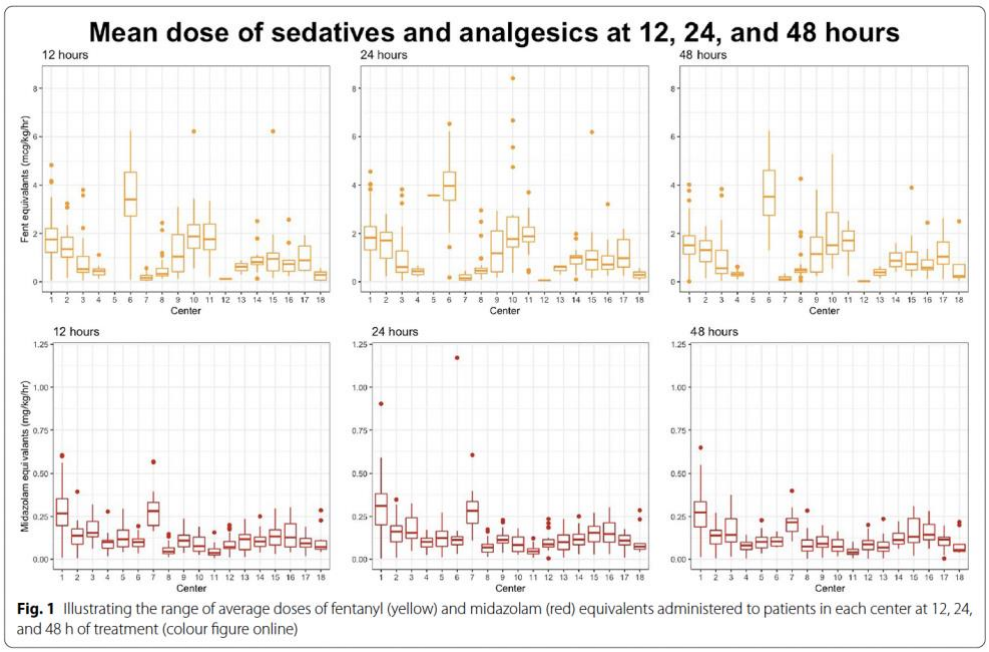

Fig. 1 Illustrating the range of average doses of fentanyl (yellow) and midazolam (red) equivalents administered to patients in each center at 12, 24, and 48 h of treatment (colour figure online)

Figure 2. Illustrating the range of average doses of fentanyl (yellow) and midazolam (red) equivalents administered to patients in each center at 12-, 24-, and 48- hours of treatment.

Dosage and titration of sedatives and analgesics

Models incorporating the center effect demonstrated significantly improved performance for sedation and analgesia dosing predictions at all time points ($p < 0.001$). Including the center effect increased the R^2 values for sedation and analgesia models from less than 10% to approximately 50%.

Significant differences in the titration of fentanyl dosage were observed between 12 and 24 hours ($p = 0.04$) and 24 and 48 hours ($p < 0.001$). Importantly, a decrease in fentanyl dosage between 24 and 48 hours was associated with improved six-month survival ($p = 0.048$).

Awakening

Of the 364 patients alive at the end of the study, 342 had a registered awakening time. Early awakening was rare, with only 4 patients (0.7%) awake on the first day and 20 patients (3.3%) awake on the second day. Late awakening was associated with higher average fentanyl dosage at 48 hours, a relationship that was significant both with ($p = 0.002$) and without ($p = 0.003$) the inclusion of the center effect. Additionally, an increase in fentanyl titration between 24 and 48 hours was

associated with late awakening ($p = 0.04$ without center effect, $p = 0.005$ with center effect). Similarly, increased midazolam titration during the same period was strongly associated with late awakening ($p < 0.001$ in both models).

Clinical seizures

An increase in midazolam equivalent dosing between 24- and 48- hours was significantly associated with clinical seizures ($p = 0.04$).

Survival

There were significant associations between decreased titration of analgesics and survival at 6 months ($p = 0.048$).

Model adjustments and robustness of findings

These findings remained consistent across models that adjusted for clinically relevant variables, including age, sex, time to ROSC, bystander CPR, shockable rhythm, shock on admission, target temperature, and center effect.

Paper II

Patient population, clinical characteristics, and outcomes

The study included 1861 patients, with a majority being male (79.4%) and a mean age of 63.8 years (SD ± 13.6). Most patients experienced an initial shockable rhythm (73.7%) and received bystander cardiopulmonary resuscitation (79.9%). The mean time to ROSC was 30.7 minutes (SD ± 20.1). Among clinical outcomes, 47% of patients achieved a good neurological recovery (mRS 0-3) at six months, and 51% survived to 6 months. Clinical seizures occurred in 25% of patients during their intensive care unit stay, and the median time to awakening was 2.5 days (IQR 1.8-4.4). Patients in the hypothermia group had a significantly higher use of NMB (66% vs. 45%, $p < 0.001$) compared to the normothermia group, though other sedation and analgesia practices were similar across groups.

Sedation and analgesia practices

Propofol was the most commonly administered sedative, given to 86% of patients within the first 72 hours. Midazolam was used in 36%, fentanyl in 50%, and remifentanil in 33% of the cohort. The cumulative doses of sedatives and analgesics did not significantly differ between the hypothermia and normothermia groups, but NMB was more frequently administered in the hypothermia group (66% vs. 45%, $p < 0.001$).

Dose-dependent effects of sedatives on outcomes

Initial analyses using chi-square analyses demonstrated significant associations between propofol dose and clinical outcomes. These analyses indicated that higher total doses of propofol were significantly associated with good neurological recovery ($p < 0.01$), 6-month survival ($p = 0.001$), clinical seizures ($p < 0.001$), and late awakening ($p < 0.001$). These findings established the foundation for further analysis of dose-response relationship. Subsequent demonstrated of propofol dose quartiles showed nuanced association with outcomes:

- Good neurological outcomes (mRS 0-3 at 6 months) were associated with moderate propofol doses (100.7-153.6 mg/kg), with an odds ratio (OR) of 1.62 (95% CI 1.12-2.35).
- Survival was associated with low and moderate propofol doses (0.01-100.6 mg/kg) with an OR of 1.49 (95%CI 1.05 - 2.12) and OR 1.83 (95% CI 1.27-2.65), respectively.
- Clinical seizures were associated with low, moderate, and high propofol doses (0.01-669.4 mg/kg) with OR of 1.53 (95%CI 1.06 - 2.2), OR 1.56 (95% CI 1.06-2.29), and OR 2.82 (95% CI 1.95-4.11), respectively.
- Late awakening was significantly associated with high propofol doses (153.7-669.4 mg/kg), (OR 3.19, 95% CI 1.91-5.42).

Effects of analgesics on outcomes

Fentanyl and remifentanil, both short-acting analgesics, were associated with better outcomes:

- Fentanyl use was associated with good neurological outcomes (OR 1.69, 95% CI 1.27-2.26) and survival (OR 1.80, 95% CI 1.35-2.40).
- Remifentanil showed similar positive associations for neurological outcomes (OR 1.50, 95% CI 1.11-2.02) and survival (OR 1.56, 95% CI 1.16-2.10).

Effects of midazolam on outcomes

- The use of midazolam was positively associated with clinical seizures (OR 1.99, 95% CI 1.52-2.61) and late awakening (OR 1.98, 95% CI 1.38-2.86).

Sensitivity analyses: Comatose patients at 96 hours without seizures

Among the subgroup of 463 comatose patients at 96 hours without clinical seizures:

- Good neurological outcomes (mRS 0-3 at six months) were associated with moderate and high propofol doses (1.86-38.86 mg/kg) with an OR of 3.15 (95% CI 1.29 - 8.06) and OR 2.78 (95% CI 1.15 - 6.99), respectively.

- Survival was associated with high and moderate doses of propofol (1.86-38.86 mg/kg) with an OR of 3.43 (95% CI 1.43 - 8.59) and OR 3.27 (95% CI 1.38 - 8), respectively.
- Fentanyl and remifentanil use were associated with good functional outcome and survival. Fentanyl had an OR of 2.2 for good functional outcomes (95% CI 1.1-4.4) and 2.7 for survival (95% CI 1.3-5.4). Remifentanil had an OR of 2.2 (95% CI 1.1-4.5) and 2.2 for survival (95% CI 1.1-4.5).

Paper III

Patient population

The study enrolled 71 patients who were randomized to receive either hypothermia (target temperature of 33°C) or normothermia (target temperature <37.8°C) following OHCA. Baseline characteristics and severity of illness were comparable between the two groups, ensuring a balanced study population.

Sedative and analgesic administration and blood concentrations

There were no significant differences between the hypothermia and normothermia groups in terms of the cumulative doses or serum concentrations of sedative and analgesic drugs administered during the study period, including at the end of TTM intervention (40h), or at the end of protocolized fever prevention phase (72h), see figure 3. This included commonly used medications such as propofol, midazolam, clonidine, dexmedetomidine, morphine, oxycodone, ketamine, and esketamine.

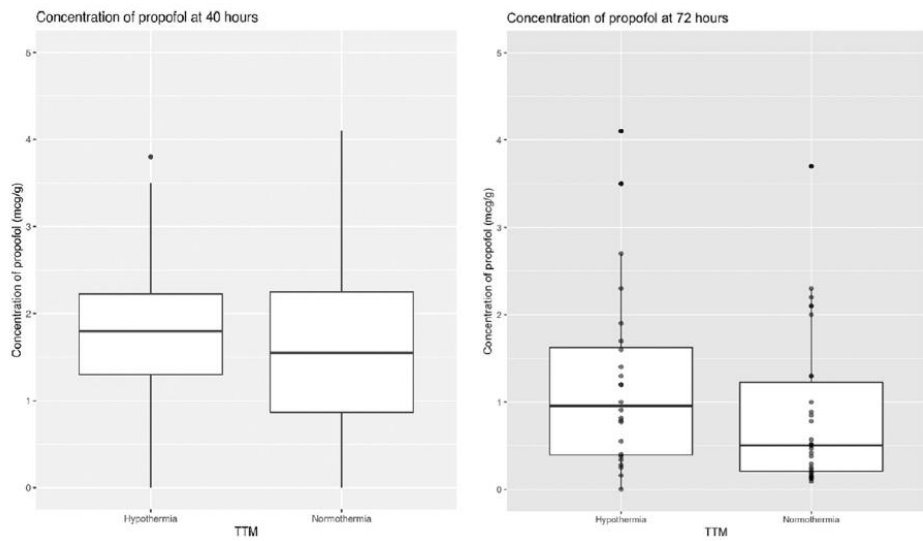

Figure 3. Boxplot of serum concentrations of propofol at 40 and 72 hours. Median serum concentrations of propofol at 40 hours were 1.80 (1.30, 2.30) in hypothermia patients compared to 1.60 (0.95, 2.30) normothermia patients, p = 0.2. Median serum concentrations of propofol at 72 hours were 0.96 (0.40, 1.63) in hypothermia patients compared to 0.51 (0.21, 1.23) in normothermia patients, p = 0.10. Two outliers not shown in the figure with concentration of 6,9 mcg/g (hypothermia) and 24,0 mcg/g (normothermia) at 40 hours.

Time to awakening and neurological outcomes

The median time to awakening was 53 hours in the hypothermia group and 46 hours in the normothermia group. While this represented a trend toward faster awakening in the normothermia group, the difference did not reach statistical significance (p = 0.09), see Figure 4. Neurological outcomes assessed at six months follow-up showed no significant differences between the two groups.

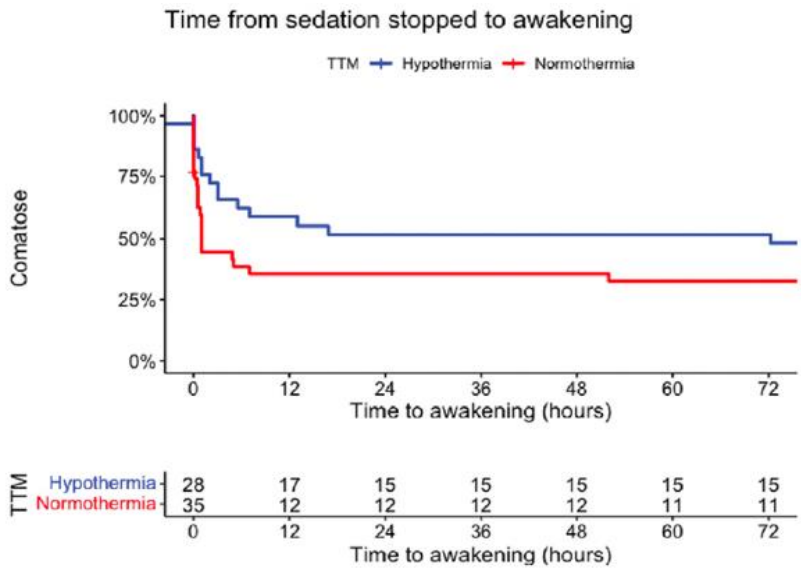

Figure 4. Time from sedation stopped to awakening in patients receiving propofol and midazolam. The time from sedation discontinued to awakening was analyzed using log rank test and showed no significant difference in time to awakening between normothermia and hypothermia groups, p = 0.1.

Paper IV

Study inclusion and characteristics

A systematic search yielded 17621 publications, of which 15 trials met the inclusion criteria, encompassing a total of 4352 participants, see Figure 5. Funnel plot analysis demonstrated minimal risk of publication bias, as indicated by Egger's statistics (intercept: -0.1953, standard error: 0.56, p = 0.73). Of the included trials, four (2084 participants) compared no sedation with sedation, while eleven (2268 participants) compared different levels of sedation, including daily interruption versus

continuous sedation, intermittent versus daily interruption, and lighter versus deeper sedation. Additionally, four trials specified the sedative type, comparing dexmedetomidine with other sedatives.

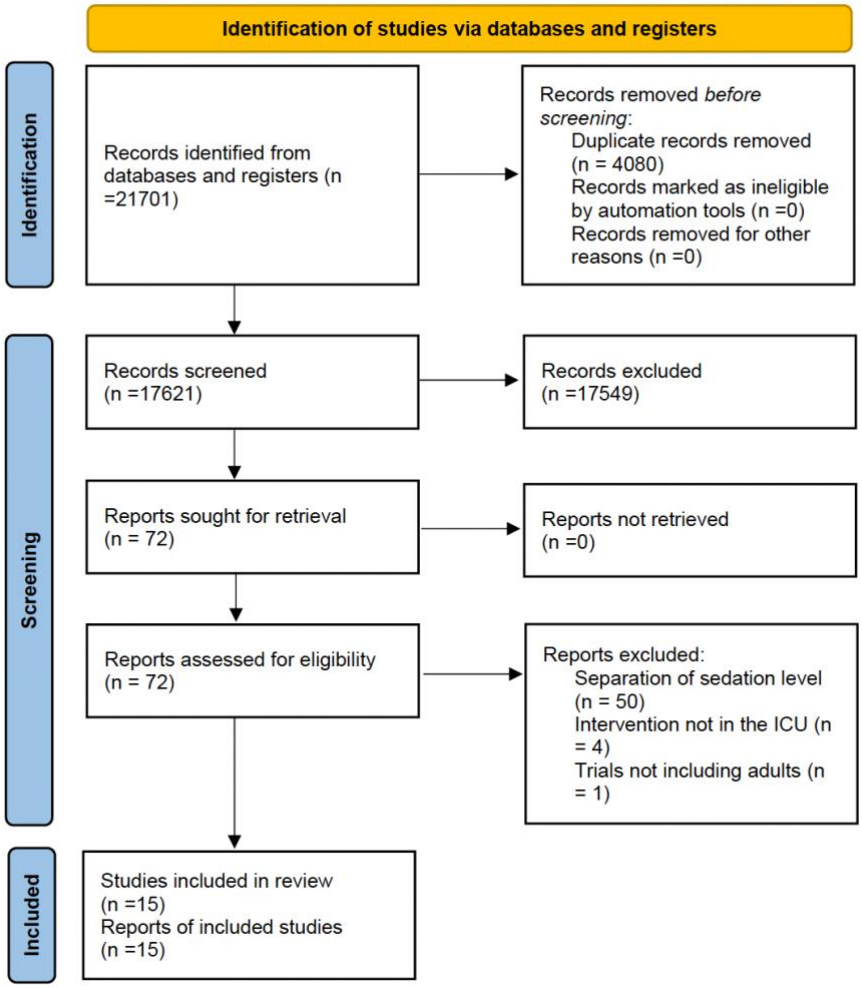

Figure 5. Prisma flow diagram outlining study inclusion.

Primary outcome: All-cause mortality

All 15 trials reported data on all-cause mortality. Mortality rates were 33.9% (739/2177) in the lighter sedation group and 34.3% (748/2175) in the deeper sedation group. A meta-analysis revealed no significant difference in mortality between the two groups (RR 0.94, 95% CI 0.83-1.06; $I^2 = 20\%$; p = 0.28), see figure 6. TSA indicated that a relative risk reduction of 16% or more is unlikely. The certainty of evidence for this outcome was rated as moderate, due to the high risk of bias across many trials.

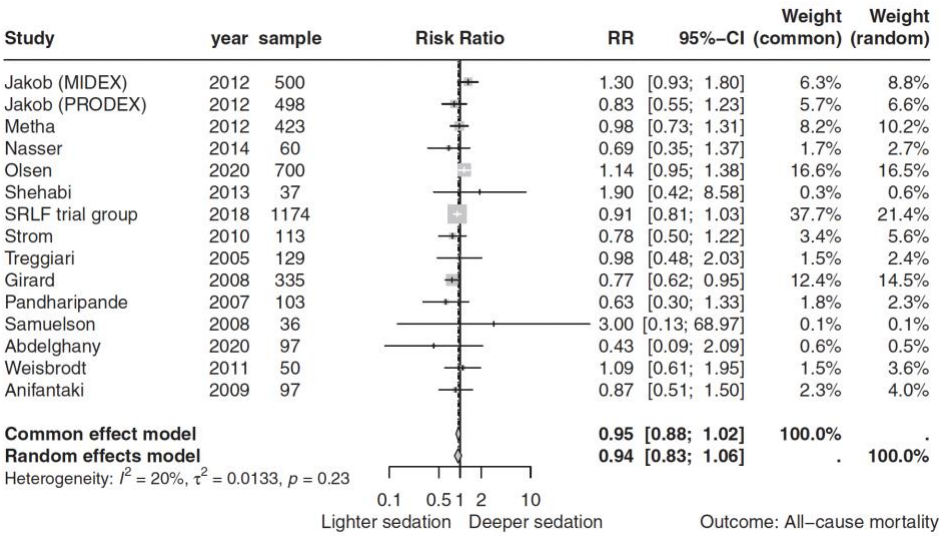

Figure 6. Random effects meta-analysis comparing lighter sedation versus deeper sedation for all-cause mortality. Random effects meta-analysis comparing lighter sedation versus deeper sedation for all-cause mortality (risk ratio 0.94, 95% confidence interval 0.83–1.06; p-val = 0.23; I2 = 20%; 15 trials). The risk ratios show a favor of lighter sedation to the left and deeper sedation to the right.

Secondary outcomes

Serious adverse events were reported in all 15 trials, with an incidence of 40.6% (883/2177) in the lighter sedation group and 41.1% (893/2,175) in the deeper sedation group. Meta-analysis showed no significant difference between the groups (RR 0.99, 95% CI 0.92-1.06; $I^2 = 0\%$; p = 0.80). TSA analysis concluded that a relative risk reduction of 9% or more is unlikely.

Delirium was assessed in 11 trials involving 3368 participants, using various diagnostic tools. The incidence was 33.9% (570/1681) in the lighter sedation group and 33.2% (561/1687) in the deeper sedation group. Meta-analysis showed no significant difference in delirium rates between the groups (RR ratio 1.01, 95% CI

0.94-1.09; p = 0.78). TSA suggested that a relative risk reduction of 12% or more is unlikely.

No trials reported on neurological outcome.

Exploratory outcomes

The duration of mechanical ventilation was reported in five trials (1024 participants). The meta-analysis found no significant difference between groups, with a mean difference of -0.91 days (95% CI -2.01 to 0.18; p = 0.10). Three studies (198 participants) reported on the incidence of PTSD which was 8.6% in the lighter sedation group and 8.8% in the deeper sedation group. Meta-analysis showed no significant difference between the groups (RR 0.97, 95% CI 0.33-2.85; p = 0.95).

Risk of bias and GRADE assessment

Thirteen trials were assessed as having a high risk of bias, primarily due to the lack of blinding. Only two trials were deemed to have a low risk of bias. The GRADE assessment rated the certainty of evidence as moderate for mortality, serious adverse events, and delirium, reflecting concerns about the methodological limitations of the included trials, see Table 6. The certainty for exploratory outcomes varied depending on the quality and quantity of the available data.

Table 6. Summary of findings table for lighter sedation versus deeper sedation.

Lighter sedation compared to deeper sedation in critically ill adult patients.

Patients or population: Critically ill adult patient admitted to intensive care unit.
Setting: Admitted to intensive care unit.
Intervention: Lighter sedation.
Control: Deeper sedation.

Outcome	Anticipated absolute effect size (95% CI)[c]		Relative effect size (95% CI)	No of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with control	Risk with intervention				
All-cause mortality (follow up range: 28 days–365 days)	343 per 1000	339 per 1000	RR: 0.94 (0.83, 1.06)	4352 (15 RCT)	Moderate[a]	Risk of bias: Serious Inconsistency: No Indirectness: No Imprecision: No Publication bias: No
Serious adverse events (follow up range: 28 days–365 days)	411 per 1000	406 per 1000	RR: 0.99 (0.92, 1.06)	4352 (15 RCT)	Moderate[a]	Risk of bias: Serious Inconsistency: No Indirectness: No Imprecision: No Publication bias: No
Delirium (follow up range: 7 days–45 days)	332 per 1000	339 per 1000	RR: 1.01 (0.94, 1.09)	3368 (11 RCT)	Moderate[a]	Risk of bias: Serious Inconsistency: No Indirectness: No Imprecision: No Publication bias: No
PTSD (follow up range: 4 weeks-2 months)	88 per 1000	85 per 1000	RR: 0.97 (0.33, 2,85)	138 (2 RCT)	Low[a,b]	Risk of bias: Serious Inconsistency: No Indirectness: No Imprecision: yes Publication bias: No

RR: Risk ratio CI: Confidence interval; GRADE: GRADE Working Group grades of evidence. GRADE Working Group grades of evidence. High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. Explanations: [a]Downgraded one for risk of bias. [b]Downgraded one for imprecision due to small sample size and wide confidence intervals. [c]The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Discussion

This thesis synthesizes findings from five studies to provide comprehensive insights into the impact of sedation and analgesia management strategies in intensive care, particularly focusing on OHCA and intensive care unit practices. The discussion is structured around the key research questions addressed in the studies, highlighting common themes and subjects.

Paper I and II

Sedation and analgesia practices

The sedation and analgesia practices observed in the TTM- and TTM2- trials demonstrate a reliance on both short-acting agents (e.g., propofol and remifentanil) and long-acting agents (e.g., midazolam and fentanyl) during and after TTM following OHCA. While current guidelines recommend short-acting sedatives and analgesics to facilitate earlier awakening, assessment of level of consciousness, and to facilitate neurological prognostication, long-acting agents remain widely used [45, 47]. Propofol was the most frequently used sedative in both trials, but midazolam was also common. These findings reveal the balance between achieving optimal sedation depth, reducing adverse effects, and adhering to guideline-based practices. Despite recommendations to discontinue sedation early to allow accurate neurological assessment with the use of propofol and remifentanil, the frequent use of midazolam and fentanyl suggests variability in practice that may stem from differences in local expertise, resource availability, and patient-specific factors such as shivering, seizures, and hemodynamic instability.

Sedation and analgesia practices over time

In the TTM-trial, sedation and analgesia practices predominantly relied on long-acting drugs, with 42% of patients receiving midazolam and 51% receiving fentanyl. Propofol was used in 70% of patients, while remifentanil was administered to only 16%, reflecting its limited adoption during this earlier trial. In contrast, the TTM2-

trial showed a significant shift toward short-acting agents, with 86% of patients receiving propofol and 36% received midazolam. Additionally, remifentanil use was 33%, indicating a move away from fentanyl as the dominant analgesic. This highlights that practices are considering the adverse effects of prolonged sedation and adopting of guidelines recommending short-acting agents to reduce sedation duration, facilitate early neurological prognostication, and optimize recovery. Additionally, the results from the TTM2-trial emphasizes that sedation practices have evolved between TTM- and TTM2- trials, reflecting the broader adoption of normothermia protocols and the growing recognition of the risks associated with prolonged deep sedation, such as delayed awakening and confounding in neurological prognostication. These changes underscore an improvement within the field, driven by emerging evidence and evolving clinical practices.

Variation in sedation and analgesia practices across centers

In the large randomized clinical TTM-trial, we found significant differences in the approach to providing sedation and analgesia. The treatment center was independently and strongly associated with the number of medications given, cumulative dosing, and titration of sedatives and analgesics, during and immediately following temperature management. Importantly, treatment center remained independently associated for dosing and titration after adjustment for target temperature and clinically relevant variables, including markers of severity of illness like initial heart rhythm and total ischemic time. This suggests that local protocols influence sedation and analgesic dosing more than patient factors. This variability highlights the need for further research to better define the optimal sedation strategies for TTM patients and ensure consistent application across centers. The TTM-trial suggest that institutional factors, including clinician training, protocol adherence, and resource availability, may explain much of this heterogeneity. For example, centers with more experience or access to advanced monitoring tools may favor short-acting agents and early awakening protocols, while others may rely more heavily on traditional approaches involving midazolam or fentanyl.

Sedation practices and target temperature management

The level of target temperature (33 °C vs. 36 °C) did not significantly influence overall sedation dosing during the initial 48 hours of therapy in the TTM-trial, notably, some differences emerged in the titration of analgesics, with increased titration observed between 12 and 24 hours at a target temperature of 36 °C. This may reflect efforts to manage discomfort or shivering in the group managed at 36 °C, where active cooling is less intense. Similarly, in the TTM2-trial there were no

statistically significant differences in sedation or analgesia dosing up to 72 hours between patients treated with hypothermia or normothermia, suggesting that doses to keep the patients at deep sedation during TTM were similar.

Impact of sedation management and clinical outcomes

Late awakening

The findings from the TTM- and TTM2- trial show an association between higher total doses and titration of sedatives and analgesics with late awakening, after adjustment for clinical and severity of illness factors. Specifically, in the TTM-trial, higher doses of analgesics at 48 hours and increased titration of analgesics between 24 and 48 hours were significantly associated with delayed awakening. Opioid analgesics, in particular, may blunt the response to painful stimuli in the GCS and impair the pupillary light reflex, which could confound neurological prognostication. Interestingly, there was no significant association between the average dosage of sedatives up to 48 hours and time to awakening which may be because most patients received short-acting sedatives.

In the TTM2-trial, higher total doses of propofol up to 72 hours and the administration of midazolam were also associated with delayed awakening, further emphasizing the relationship between sedation and analgesia management and awakening times. Although these findings strengthen the evidence, they also highlight the need for further research to determine whether these associations are a result of sedation practices, underlying patient factors, or other clinical factors.

Our findings are in concordance with other trials that found the use of midazolam-fentanyl sedation strategies to be associated with longer time to awakening post cardiac arrest [197, 198]. However, these findings also emphasize the risk of prolonged awakening times, which may increase susceptibility to premature WLST due to perceived poor neurological prognosis. This underscores the critical need to balance sedation depth with the ability to perform accurate prognostication, avoiding misinterpretation of clinical signs. Moreover, delayed awakening is common after cardiac arrest and these findings are supported by additional evidence showing that prolonged time to awakening may lead to suboptimal decision-making and adverse events in post-cardiac arrest care [180].

Clinical seizures

Clinical seizures are common after cardiac arrest, often resulting from neuronal excitation due to brain injury. Left untreated, seizures can exacerbate brain injury

through increased metabolic demand, disruption of cerebral autoregulation, and excitotoxicity, leading to poorer outcomes. Although sedatives can suppress seizures and influence cerebral oxygen consumption and blood flow, it is unclear whether they provide additional neuroprotective effects, such as acting seizure prophylactic, during TTM and post cardiac arrest care.

In the TTM-trial, increased sedative dosing between 24 and 48 hours and higher total doses at 48 hours were associated with clinical seizures, likely reflecting the clinical practice of increased sedation in response to seizure activity or discomfort during TTM. Similarly, the TTM2-trial showed an association of higher propofol doses and midazolam administration with clinical seizures. Sedatives, particularly propofol and midazolam, are known for their antiepileptic properties. However, whether these higher sedative doses reduce the risk of seizure occurrence consequently improving outcome, or simply reflect the clinical need for increased sedation during seizures, remains unclear. The causal relationship between sedation dosing and seizure occurrence remains uncertain.

Administering sedation, analgesia, and NMB during TTM and post-cardiac arrest care may make it challenging to detect clinical seizures [199]. EEG monitoring, as recommended by current guidelines, plays a crucial role in identifying seizures and is as an important prognostic indicator [97, 200]. Although routine seizure prophylaxis is not advised, antiepileptic medications and sedatives such as propofol are recommended treatments for seizures [45, 47]. Consequently, the association between higher propofol doses and clinical seizures may be due to increased sedation when seizures occur. This aligns with prior research indicating that while it is feasible to suppress epileptiform EEG activity, it does not improve outcome. The TELSTAR trial, designed to assess whether treating status epilepticus improves outcomes in comatose post-cardiac arrest patients with epileptiform patterns on continuous EEG [100]. In this trial, anti-seizure and sedative medications were administered to suppress all epileptiform activity for at least 48 hours, was compared to standard care without anti-seizure treatment. While suppression of all rhythmic and periodic patterns was achieved in 56% of patients in the intervention group versus only 2% in the control group, there was no significant difference in poor outcomes at 3 months.

Functional outcome and survival

The TTM- and TTM2- trials demonstrates insights into the complex relationship between sedation and analgesia practices and long-term functional outcomes and survival after cardiac arrest. In the TTM-trial, decreased dosing of analgesics between 24- and 48- hours was significantly associated with improved six-month survival. However, no such association was found for titration of sedatives between 24 and 48 hours or titration of sedation or analgesia between 12 and 24 hours. The

observed association between decreased dosing of analgesics and improved survival highlights the need for precise titration during the post-TTM period. However, these results may also reflect variability in center-specific practices and patient-specific factors, such as severity of brain injury, which may confound the observed associations.

In the TTM2-trial, a post-hoc analysis demonstrated a significant association between higher total doses of propofol and good functional outcomes and survival at six months. Additionally, the use of remifentanil and fentanyl was associated with improved outcomes, further emphasizing their role when managing patients with less severe brain injuries. These patients appeared to require higher doses of sedatives and analgesics for therapeutic comfort, suggesting that their less severe brain injuries allowed for a more aggressive approach to maintaining comfort during therapy. However, given the observational nature of the study, causality remains uncertain. It is possible that higher doses of sedatives and analgesics themselves contributed to neuroprotection, rather than merely reflecting the clinical status of patients with milder injuries. Propofol, for instance, has been suggested to have neuroprotective properties through mechanisms such as reducing cerebral metabolism, mitigating excitotoxicity, and by promoting glymphatic system function. Thus, while the association between higher propofol and analgesic doses with good outcomes likely reflects patient severity of illness, it is also plausible that sedative and analgesic management mat be neuroprotective and improve outcome. These findings underscore the importance of individualized sedation and analgesia strategies, not only for maintaining comfort but potentially for optimizing neuroprotection and improving survival and functional recovery.

Reasons for prolonged or increased sedation

The dosing data collected at 48 hours in the TTM-trial and at 72 hours in the TTM2-trial may depend on the clinical context of patients requiring prolonged sedation beyond the mandatory periods of 36- and 40-hours sedation, respectively. While both protocols recommended discontinuation or tapering of sedation as soon as possible after these mandatory periods, the decision was left to the discretion of the treating physician. The reasons for prolonged sedation remain multifactorial and complex, reflecting the variability in clinical practices across centers and patient-specific needs.

One potential reason for increased sedation and analgesia is the management of shivering, a physiological response that is closely monitored during TTM. Shivering is associated with improved outcomes after cardiac arrest, as it may indicate preserved thermoregulatory mechanisms and less severe brain injury and has been associated with better survival and neurological recovery in previous studies [201]. However, if left untreated, shivering can increase metabolic demand and contribute

to secondary brain injury. To manage this, sedation dosing is often escalated as a first-line therapy, and NMB may be introduced for refractory cases [202]. Adequate sedation must accompany NMB use to prevent awareness during induced paralysis. This escalation in sedation may partly explain the higher doses observed in patients with good functional outcomes and survival.

Another reason for prolonged sedation could be the presence of frequent myoclonus, which often indicates more severe brain injury and necessitates continued sedation and analgesia. Additionally, prolonged mechanical ventilation is a common clinical scenario requiring extended sedation, as sedation helps facilitate patient-ventilator synchrony and comfort. These factors may contribute to the observed associations between sedation practices, late awakening, clinical seizures, and survival.

Recognizing the heterogeneity, recent efforts have focused on patient phenotyping to identify subgroups with distinct treatment responses. Machine learning approaches and multimodal monitoring techniques are increasingly being explored to stratify patients and tailor post-arrest interventions accordingly [203, 204]. These advancements hold promise for optimizing sedation strategies by integrating real-time physiological data and predictive modeling into clinical decision-making. While the field is still evolving and definitive answers remain elusive, addressing heterogeneity in post-arrest care could be a key step toward improving individualized treatment strategies. This discussion also provides a conceptual foundation and highlights the importance of future research aimed at refining sedation and analgesia practices based on patient-specific factors.

Strengths and limitations

This thesis integrates findings from the TTM- and TTM2- trials, representing the most comprehensive evaluations to date of sedation and analgesia management after OHCA. The trials benefit from large, diverse patient cohorts across multiple international centers, which strengthens the generalizability of the findings. By utilizing individual patient data and robust adjustments for illness severity, the analyses provide valuable insights into factors influencing outcomes such as functional recovery, survival, delayed awakening, and clinical seizures. Although we adjusted for key clinical variables and illness severity in the multivariable analysis, there may still be residual confounding. For instance, the TTM-trial lack data on important confounding factors such as organ dysfunction, including liver and kidney impairment, which may influence drug clearance. Additionally, information on NMB use and shivering, both critical factors affecting sedation requirements, was not collected. In the TTM2-trial, while the use of neuromuscular blockade was included in the multivariable models to account for their potential impact, the depth and duration of neuromuscular blockade were not recorded. Additionally, EEG recordings were not uniformly available across participating

centers in neither TTM- nor TTM2- trials and were therefore not included in these studies which may have introduced heterogeneity in seizure detection.

Variation in sedation and analgesia practices across the 61 participating centers in the TTM2-trial may represent a source of residual confounding not fully captured by the current multivariable model. Although the TTM2-trial protocol was standardized across sites, recommending a target for sedation depth (RASS –4 to –5) and the use of short-acting agents, differences in clinical practice may still be a source of residual confounding.

Furthermore, neither TTM- nor TTM2- trials were specifically designed to investigate sedation and analgesia management. As such, there is a risk of post-randomization bias, particularly related to differences in clinical management not captured by available data. In the TTM-trial, sedation and analgesia data were collected retrospectively. This introduced variability, as not all centers participated, and only 623 of 939 patients had complete data, raising concerns about responder bias. For example, patients without sedation data had significantly lower rates of good neurological outcomes (42% vs. 49%), likely reflecting site-related differences. To mitigate potential information bias, data in the TTM2-trial was collected prospectively using standardized case report forms across all sites.

In the TTM-trial, cumulative doses were collected at 12- , 24- , and 48- hours, despite the mandatory intervention ending at 36 hours. Similarly, in the TTM2-trial, cumulative sedation doses were collected at 72 hours despite the protocol specifying mandatory sedation for 40 hours. The reasons for prolonged sedation or titration were not recorded in neither TTM- nor TTM2- trial. To address this limitation, sensitivity analyses in the TTM2-trial provide deeper understanding of sedation practices in important patient subpopulations, such as those remaining comatose at 96 hours without seizures.

The observational nature in both TTM-trials should be further investigation to establish the causality of the associations found, and findings should be interpreted as hypothesis-generating. Despite these limitations, this work provides an important foundation for understanding sedation practices and their impact on post-cardiac arrest outcomes.

Paper III

Effects of temperature management on sedation and pharmacokinetics during TTM in post-cardiac arrest care

This study, as part of the TTM2-trial, represents one of the most comprehensive evaluations to date on the serum concentrations of sedatives during post-cardiac arrest care. It adds important insights into the interaction between sedation practices, temperature management, and clinical outcomes.

Sedation and serum concentrations

We found no statistically significant differences in administered doses or serum concentrations of sedatives and analgesics between hypothermia and normothermia groups at any investigated time point when correcting for confounders. However, the hypothermia group showed higher median administered doses of propofol (over 50% higher between 40–72 hours) and nearly double serum concentrations at 72 hours compared to normothermia. These findings align with previous studies suggesting that hypothermia slows the metabolism and lower clearance of sedatives, likely due to reduced hepatic blood flow and effects on the cytochrome P450 system [167, 170, 198, 205]. Similarly, Bjelland et al. found lower clearance of propofol, fentanyl, and morphine, but not midazolam, during TTM compared to normothermic ICU patients, while another study observed decreasing serum concentrations of remifentanil, propofol, and midazolam with rewarming, though fentanyl concentrations remained stable [170, 205]. These pharmacokinetic variations, though based on small cohorts, suggest that hypothermia may prolong drug effects, necessitating careful interpretation of sedation depth and neurological prognostication.

For midazolam, a small subset of patients managed at hypothermia exhibited significantly longer awakening times, which may be explained by its slower elimination compared to propofol. Although renal function was similar between groups, individual factors such as the degree of brain injury and metabolic clearance rates likely contributed to these differences. Given these findings, the lingering effects of sedation, regardless of TTM level, should be considered when assessing neurological recovery and making decisions on WLST.

Shivering and seizures

Shivering was more prevalent in the hypothermia group ($p = 0.003$), consistent with prior findings from the TTM2-trial. Shivering likely influenced the increased

propofol doses observed during the intervention period (0-40 hours), as escalation of sedation is standard protocol for managing shivering to prevent secondary brain injury. Beyond 40 hours, however, shivering was no longer associated with increased sedation, suggesting other factors drove sedation needs during prolonged care.

Seizures were more common in the hypothermia group (p=0.015) and may indicate more severe brain injury in these patients, as levels of neuron-specific enolase were slightly higher (42 vs 28, p=0.068). However, sedation doses did not significantly differ between patients with and without seizures, suggesting that AED effectively controlled seizures without requiring additional sedation.

Implications for clinical practice

This study supports the hypothesis that pharmacokinetics during TTM is influenced by temperature but do not significantly impact time to awakening in most patients, excluding those receiving midazolam. Although hypothermia is associated with slower clearance of sedatives, the level of TTM itself was not a predictor of serum concentrations when corrected for confounders. This suggests that other clinical variables, such as the severity of brain injury, organ failure, shivering, and the use of NMB, play key roles in determining sedation requirements and the timing of neurological prognostication. As such, these factors should be carefully evaluated alongside pharmacologic considerations before making decisions regarding WLST.

Limitations

Despite the strengths of this study, including its multicenter cohort and prospective data collection, several limitations must be acknowledged. The study was not primarily designed to evaluate sedation and analgesia, and sedation data were collected as a secondary outcome. Reason of prolonged sedation beyond the mandatory periods of 40 hours were not collected, limiting our ability to fully contextualize dosing patterns and time to awakening. The small sample size of patients restricts the generalizability of findings, lowers the statistical power of the study, and individual patient factors such as drug metabolism rates and degree of brain injury were not fully accounted for. Additionally, while shivering and seizure data were analyzed, subclinical seizures, which may affect sedation needs, were not captured.

Paper IV

This systematic review and meta-analysis of 15 RCTs involving 4352 participants represents one of the most comprehensive evaluations of sedation depth in critically ill adults. The findings indicate that the level of sedation does not appear to significantly affect the risk of death, serious adverse events, delirium, or post-traumatic stress disorder. Similarly, no effect on the duration of mechanical ventilation was observed. These results are supported by a lack of statistical heterogeneity and consistent findings across predefined subgroup analyses, reinforcing the robustness of the conclusions. Additionally, the TSA strengthened the robustness of these findings by demonstrating futility, indicating that additional trials with similar methodologies are unlikely to affect the results. However, these conclusions were based on calculated effect sizes of 9 and 16%. Thus, future trials should aim to address the limitations of current evidence by using more robust methodologies to investigate the effect of sedation depth on outcomes and in larger sample sizes aiming for realistic intervention effects. Understanding the impact of sedation depth is crucial for optimizing patient outcomes and guiding clinical practice ICUs.

Strengths of the study

The study utilized a rigorous methodology, predefined in detail, and the protocol was published ahead of performing the literature search and adherence to predefined protocols. The inclusion of diverse sedation strategies and detailed subgroup analyses enhance the study's generalizability. We searched all relevant databases and used an eight-step assessment suggested by Jakobsen and colleagues to assess our results' clinical significance [206]. TSA was used to assess the risk of type I and II errors, ensuring a high level of analytical rigor. By rejecting a relative risk reduction of 16% or greater, the TSA findings suggest that additional trials are unlikely to significantly alter the conclusions. Furthermore, we did meta-analyses with both fixed effects and random effects meta-analysis, we investigated subgroup differences, and we assessed the certainty of the evidence using GRADE.

Methodological challenges and limitations

Despite its strengths, several limitations must be acknowledged. Thirteen of the fifteen included RCTs had a high risk of bias, primarily due to deviations from intended interventions, lack of blinding, and subjective outcome assessments. Treating clinicians and outcome assessors were often aware of patients' targeted sedation levels, potentially influencing sedation dosages and other treatments. Additionally, the methodological variations in defining and achieving sedation

levels, such as differences in sedation scales, protocolized sedation, or no sedation, make direct comparisons challenging. For example, some studies compared no sedation to sedation with daily interruptions, while others evaluated continuous versus intermittent sedation. This variability complicates the interpretation of the results. This limitation was address using subgroup analyses according to the approach used to define and reach the targeted sedation level, which strengthened our results.

Further, the evidence on neurological outcomes and quality-of-life remains insufficient, particularly for vulnerable populations such as post-cardiac arrest and brain-injured patients, who were often excluded from the included trials and lack of reporting of these patient-important outcome. These patient groups pose unique challenges in sedation management, such as altered consciousness and difficulties in assessing sedation levels, highlighting a gap in the evidence base. Additionally, the lack of high-quality data on delirium, a secondary outcome, reflects inconsistencies in assessment methods across studies.

The risk of bias assessment revealed that all but two studies were at high risk of bias, primarily due to the lack of successful blinding of treating clinicians, thus introducing potential bias through deviations from the intended interventions. The GRADE assessment rated the certainty of the evidence for the primary outcomes as moderate, indicating that further research could impact the confidence in the effect estimates. These considerations should be considered when interpreting the findings and their implications.

Implications for practice

The findings challenge the assumption that lighter sedation improves outcomes. While current guidelines recommend lighter sedation to enhance short-term recovery, this study suggests that lighter nor deeper sedation may not confer significant benefits in terms of mortality or other selected outcomes. Instead, sedation strategies should be individualized, considering patient-specific factors such as the severity of illness, underlying conditions, and clinical context. The findings are particularly relevant for populations with acute brain injury and patients requiring TTM or with severe neurological injuries, where sedation practices must balance patient comfort with neurological assessment and prognostication. The results also highlight the need to consider broader implications, such as the recourse utilizing and impact of sedation strategies and the variability in patient responses to sedation.

Paper V

Aim and rationale

The SED-CARE trial investigates the effects of deep versus minimal sedation on outcomes in resuscitated OHCA patients. By comparing these two sedation strategies, the trial aims to evaluate their impact on mortality, functional outcomes, serious adverse events, and patient-reported health. The findings are expected to provide valuable evidence to refine sedation protocols tailored to the unique needs of cardiac arrest patients, improving care, optimizing outcomes, and enhancing resource utilization. SED-CARE is part of the broader STEPCARE trial, which examines the effects of mean arterial pressure targets and fever treatment with or without temperature control devices in a factorial design, further expanding the evidence base for post-cardiac arrest care.

Sedation has been an integral part of post-cardiac arrest care since the introduction of therapeutic hypothermia over 20 years ago. However, limited evidence exists to guide clinicians in determining optimal sedation depth. Sedation carries both risks, such as impaired circulation and ventilation, and potential neuroprotective benefits. It also complicates neurological prognostication, increasing the risk of premature WLST based on inaccurate neurological assessments. The SED-CARE trial addresses this critical gap, providing essential data to inform sedation strategies in cardiac arrest patients.

Potential consequences

The trial's two sedation strategies pose distinct risks and benefits. In the minimal sedation group, patients may experience anxiety, pain, discomfort, non-planned extubation, and post-traumatic stress disorder, potentially impairing neurological recovery. Conversely, the deep sedation group may face prolonged mechanical ventilation, venous thromboembolism, infections, sepsis, arrhythmias, and extended ICU stays. Furthermore, lingering effects of deep sedation may interfere with neurological prognostication, leading to suboptimal clinical decisions.

In clinical practice, cardiac arrest patients are typically managed with sedation depths similar to those in the deep sedation group, whereas the minimal sedation group mimics the management of non-cardiac arrest ICU patients. By collecting detailed data on these outcomes, the trial aims to investigate these sedation strategies and their implications.

Strengths

The SED-CARE trial has several key strengths. Its large sample size and broad inclusion criteria enhance generalizability and enable robust subgroup analyses to identify patient populations that may benefit from different sedation targets. Additionally, the trial employs patient-centered outcomes and rigorous blinding protocols, including the blinding of outcome assessors, prognosticators, statisticians, and the steering group. This minimizes bias and strengthens the validity of the results. The factorial design within the STEPCARE trial, while inherently complex, allows for simultaneous evaluation of sedation strategies alongside other critical interventions, providing a comprehensive approach to post-cardiac arrest care.

Limitations

Despite its strengths, the trial has limitations that warrant consideration. Interaction effects between the sedation intervention and the temperature or blood pressure interventions in the STEPCARE trial are an inherent feature of factorial designs. Sedation can influence cardiovascular parameters, which may interact with other interventions. Although feasibility studies have demonstrated the safety of these interventions, the trial cannot fully eliminate the risk of interactions. A sample size adjustment (6.8%) has been incorporated to account for potential loss to follow-up and minor interaction effects, minimizing their impact.

Another challenge arises from the inclusion of severely critically ill and brain-injured patients, whose baseline severity may lead to assessed sedation levels that are toward deep sedation, regardless of the sedation administered and assigned intervention. Similarly, patients in the minimal sedation group who require seizure control or temperature devices may receive increased sedation, potentially blurring the distinction between groups. To address this, the trial will conduct sensitivity analyses to explore subgroups affected by these confounders.

Unblinding of sedation targets is another limitation, as clinicians must be aware of the allocated sedation strategy. However, rigorous blinding of key stakeholders, outcome assessors, statisticians, prognosticators, and the steering group, will mitigate bias in data interpretation and ensure that trial outcomes remain objective.

Conclusions

This thesis has explored key aspects of sedation practices in post-cardiac arrest care, highlighting the variability, outcomes, and gaps in evidence across five comprehensive studies:

Paper I: Significant differences were observed between centers in the choice, dosing, and titration of sedative and analgesic drugs during and immediately following TTM. Higher dosages and upward titration were associated with delayed awakening and higher incidence of clinical seizures, while downward titration of analgesics was associated with improved survival at six months. These findings emphasize the need for standardized sedation protocols and prospective trials to further elucidate these findings and confirm causality.

Paper II: Higher doses of propofol were significantly associated with good functional outcomes and survival at six months, clinical seizures, and late awakening. Remifentanil and fentanyl were associated with good functional outcomes and survival, while midazolam was associated with clinical seizures and delayed awakening. These findings may reflect the severity of illness, with higher doses in patients with less severe brain injury and better outcomes. Although causality cannot be established, it is also possible that higher doses of sedatives and analgesics have neuroprotective effects, contributing to better outcomes.

Paper III: No significant differences were found in sedative or analgesic drug dosing, concentrations, or lingering sedative effects between patients treated with hypothermia or normothermia, unless treated with midazolam. These findings suggest that hypothermia may not significantly alter sedative pharmacokinetics or time to awakening, though further studies are needed to confirm these results in larger cohorts.

Paper IV: A systematic review and meta-analysis showed no significant differences in mortality, serious adverse events, or delirium between lighter and deeper sedation strategies in critically ill adult patients. However, the high risk of bias in most included trials and moderate certainty of evidence underscores the need for future

high-quality trials with improved methodological rigor. Addressing these limitations in future high-quality studies will be critical to optimizing sedation practices and improving outcomes for critically ill patients.

Paper V: Future Directions in the SED-CARE Trial: The SED-CARE trial, a large international study embedded within the STEPCARE trial, aims to investigate whether continuous deep sedation for 36 hours confers benefits compared to minimal sedation on six-month mortality and functional outcomes. Results from this trial will provide critical insights to refine sedation management in post-cardiac arrest care and guide future recommendations.

Future Directions

- Optimizing sedation and analgesia in acute brain injury and post-cardiac arrest patients requires balancing ICP control, seizure management, hemodynamic stability, and accurate neurological assessment. Despite growing interest in individualized sedation strategies supported by multimodal monitoring, significant variability in clinical practice reflects the lack of high-quality evidence and standardized protocols. Recent trials have not demonstrated any clear outcome benefits of specific sedative agents, highlighting the need to shift research toward evaluating sedation strategies and protocols rather than individual drugs.
- Future studies should address methodological limitations by implementing standardized sedation protocols, objective definitions of sedation depth, and blinding of participants and outcome assessors to minimize bias. Research should also focus on critically ill subpopulations, particularly post-cardiac arrest, and brain-injured patients, to ensure broader clinical applicability.
- The associations found in the TTM- and TTM2- trials between higher doses of sedatives and analgesics with improved functional outcomes, survival, and clinical seizures should be further investigated in an RCT to determine causality and whether deeper sedation has neuroprotective effects. Given the conflicting results from previous sedation trials, future research should also assess long-term functional recovery, quality of life, and cognitive function alongside short-term ICU outcomes. The SED-CARE trial will provide critical data on whether continuous deep sedation for 36 hours improves six-month survival and neurological outcomes compared to minimal sedation, shaping future post-cardiac arrest sedation management.
- Research should explore how TTM affects sedative and analgesic pharmacokinetics and its impact on time to awakening to ensure accurate neurological prognostication. A prospective trial powered to detect these differences is essential to refine sedation management and optimize post-cardiac arrest care.

Populärvetenskaplig sammanfattning på svenska

Varje år drabbas tusentals människor av hjärtstopp utanför sjukhus. Tack vare snabba insatser, såsom hjärt-lungräddning och defibrillering, kan många överleva. Många patienter hamnar i ett komatöst tillstånd och behöver intensivvård för att optimera deras chans till återhämtning. En viktig del av denna vård är sedering (nedsövning) och smärtlindring, som används för att minska obehag, förhindra skador och underlätta behandlingar som exempelvis mekanisk ventilation och temperarturbehandling.

Trots att sedering och smärtlindring är en viktig del av intensivvård efter hjärtstopp finns det begränsad kunskap om hur dessa läkemedel påverkar patientens behandling och återhämtning. Det saknas tydliga riktlinjer för vilka läkemedel som är bäst att använda, i vilken dos och under hur lång tid. Djup sedering kan ha negativa effekter såsom längre vårdtid, försenat uppvaknande, ökad risk för delirium (förvirringstillstånd) och sämre utfall. Samtidigt kan otillräcklig sedering leda till obehag och stress, vilket kan vara skadligt för hjärnan efter hjärtstopp.

Denna avhandling undersöker hur sedering och smärtlindring används vid intensivvård efter hjärtstopp och vilken påverkan det har på patienternas funktionella återhämtning, överlevnad, risk för kliniska kramper och tid till uppvaknande.

Studie I

Den första studien analyserade hur sedering och smärtlindring används vid intensivvård efter hjärtstopp. Genom att studera data från 18 sjukhus identifierades signifikanta skillnader i hur läkemedel doseras och justeras. Studien visade att högre doser av sömn- och smärtlindringsläkemedel var kopplade till en ökad risk för fördröjd uppvakning och kliniska kramper. Däremot var nedtrappning av smärtlindrande läkemedel mellan 24 och 48 timmar efter randomisering kopplad till bättre överlevnad efter sex månader.

Studie II

Den andra studien analyserade data från 1 861 patienter inom den stora TTM2-studien, som undersökte effekten av temperaturreglering efter hjärtstopp. Resultaten visade att högre doser av vissa läkemedel, som propofol, remifentanil och fentanyl, var kopplade till både bättre överlevnad och bättre funktionellt utfall. Denna studie kan inte säga om de patienter som krävde högre doser speglar graden av hjärnskadan eller om sömn- och smärtstillande läkemedel har skyddande effekter på hjärnan. Framtida studier behövs för att fastställa sambandet.

Studie III

Den tredje studien undersökte om nedkylning (hypotermi) påverkar nivåerna av sömn- och smärtlindringsläkemedel i blodet och hur det i sin tur påverkar tiden till uppvakning. Genom att analysera blodprover från patienter visade resultaten att hypotermi förlängde tiden till uppvakning hos patienter som behandlades med midazolam. Däremot påverkades inte de totala läkemedelskoncentrationerna i blodet av kroppstemperaturen.

Studie IV

Den fjärde studien var en systematisk översikt och metaanalys av 15 randomiserade kliniska studier med totalt 4 352 patienter kritiskt sjuka patienter som behandlats på intensivvården. Den analyserade hur djup respektive lätt sedering påverkar överlevnad, funktionellt utfall och risken för komplikationer såsom delirium. Resultaten visade inga signifikanta skillnader mellan djup och lätt sedering avseende dödlighet eller allvarliga komplikationer. Eftersom många av de inkluderade studierna hade brister i upplägg och endast måttlig tillförlitlighet i resultaten, behövs framtida studier med högre kvalitet och bättre metodik. Att åtgärda dessa begränsningar är viktigt för att kunna förbättra sederingsrutinerna och ge bättre vård till kritiskt sjuka patienter.

Studie V

Den femte delen av avhandlingen beskriver SED-CARE studien, en stor internationell klinisk studie som just nu pågår. Den undersöker om djup sedering (RASS -4/-5) jämfört med minimal sedering (RASS 0 till -2) påverkar dödlighet och återhämtning efter hjärtstopp. Studien omfattar 3 500 patienter och är utformad för att kunna ge tillräcklig statistisk styrka för att upptäcka en skillnad i överlevnad på 5,6%.

Slutsatser

Avhandlingens resultat ger viktig kunskap om nedsövning och smärtlindring vid intensivvård efter hjärtstopp. Studierna visar att både valet av läkemedel och mängden sömnläkemedel kan ha stor betydelse för patienternas återhämtning och utfall. Eftersom stora variationer i sövningspraxis identifierades mellan olika sjukhus, finns det behov av mer standardiserade riktlinjer för att optimera behandlingen och förbättra utfall hos dessa patienter.

Vidare visar resultaten på att högre doser av vissa sömnläkemedel kan vara kopplade till bättre funktionella utfall men samtidigt ökar risken för bieffekter, såsom längre uppvakningstid och kliniska kramper. Detta lyfter fram vikten av en noggrann balans mellan att ge tillräcklig nedsövning och att undvika djupare nedsövning.

Den pågående SED-CARE studien kommer att ge ytterligare svar på frågan om vilken strategi för nedsövning som är mest fördelaktig för dessa patienter. Genom att optimera nedsövnings- och smärtlindringsstrategier kan vi förbättra överlevnaden och livskvaliteten för patienter som genomgår intensivvård efter hjärtstopp.

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ORIGINAL WORK

Cardiac Arrest Treatment Center Differences in Sedation and Analgesia Dosing During Targeted Temperature Management

Ameldina Ceric[1*], Teresa L. May[2], Anna Lybeck[3], Tobias Cronberg[4], David B. Seder[2], Richard R. Riker[2], Christian Hassager[5], Jesper Kjaergaard[5], Zana Haxhija[1], Hans Friberg[6], Josef Dankiewicz[7] and Niklas Nielsen[1]

Abstract

Background: Sedation and analgesia are recommended during targeted temperature management (TTM) after cardiac arrest, but there are few data to provide guidance on dosing to bedside clinicians. We evaluated differences in patient-level sedation and analgesia dosing in an international multicenter TTM trial to better characterize current practice and clinically important outcomes.

Methods: A total 950 patients in the international TTM trial were randomly assigned to a TTM of 33 °C or 36 °C after resuscitation from cardiac arrest in 36 intensive care units. We recorded cumulative doses of sedative and analgesic drugs at 12, 24, and 48 h and normalized to midazolam and fentanyl equivalents. We compared number of medications used, dosing, and titration among centers by using multivariable models, including common severity of illness factors. We also compared dosing with time to awakening, incidence of clinical seizures, and survival.

Results: A total of 614 patients at 18 centers were analyzed. Propofol (70%) and fentanyl (51%) were most frequently used. The average dosages of midazolam and fentanyl equivalents were 0.13 (0.07, 0.22) mg/kg/h and 1.16 (0.49, 1.81) µg/kg/h, respectively. There were significant differences in number of medications ($p < 0.001$), average dosages ($p < 0.001$), and titration at all time points between centers ($p < 0.001$), and the outcomes of patients in these centers were associated with all parameters described in the multivariate analysis, except for a difference in the titration of sedatives between 12 and 24 h ($p = 0.40$). There were associations between higher dosing at 48 h ($p = 0.003$, odds ratio [OR] 1.75) and increased titration of analgesics between 24 and 48 h ($p = 0.005$, OR 4.89) with awakening after 5 days, increased titration of sedatives between 24 and 48 h with awakening after 5 days ($p < 0.001$, OR > 100), and increased titration of sedatives between 24 and 48 h with a higher incidence of clinical seizures in the multivariate analysis ($p = 0.04$, OR 240). There were also significant associations between decreased titration of analgesics and survival at 6 months in the multivariate analysis ($p = 0.048$).

Conclusions: There is significant variation in choice of drug, dosing, and titration when providing sedation and analgesics between centers. Sedation and analgesia dosing and titration were associated with delayed awakening, incidence of clinical seizures, and survival, but the causal relation of these findings cannot be proven.

Keywords: Cardiac arrest, Target temperature management, Analgosedation, Sedation, Analgesia, Seizures

Introduction

Cardiac arrest survivors undergo targeted temperature management (TTM) after resuscitation to reduce brain injury and improve the likelihood of a good functional

*Correspondence: ameldina.ceric@med.lu.se
[1] Division of Anesthesia and Intensive Care, Department of Clinical Sciences Lund, Helsingborg Hospital, Lund University, Svartbrödragränden 3, 251 87 Helsingborg, Sweden
Full list of author information is available at the end of the article

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outcome. This period of critical care involves dozens of clinical decisions including ventilatory strategy, hemodynamic targets, vasopressor support, organ support, and the provision of sedation and analgesia [1, 2]. Sedation and analgesia, which are almost universally provided to patients on life support and are required when patients are receiving neuromuscular blockade (NMB), have effects on patient comfort but also on hemodynamics, blood flow to the brain, and duration of mechanical ventilation, and they may reduce the occurrence of seizures and shivering during TTM [3–6]. Furthermore, it is also known that TTM alters pharmacodynamics and pharmacokinetics of most drugs including sedatives and analgesics [7–12]. Accumulation of these drugs delays awakening and confounds neurological prognostication [13]. Despite these important clinical effects, the optimal approach to analgosedation after cardiac arrest is not known.

Published guidelines give explicit recommendations on providing analgesia and sedation in the general medical and surgical intensive care unit (ICU) [14, 15], which includes frequent assessment of the level of arousal and the use of validated sedation scales. However, the post-cardiac arrest pathophysiology makes applying those recommendations to this population problematic due to the effects of global brain injury, use of TTM, unstable hemodynamics, and interference with commonly used neuoprognositcation tools [16–20].

Determining best practices in sedation and analgesia after cardiac arrest begins with the knowledge of current standards of care. General protocols and practices to provide sedation and prevent shivering have been reported [21–26], but the specific medications, doses, and titration the individual patients receive in routine clinical practice are unknown. The main purpose of this study was to evaluate the average sedation and analgesia dosing adminstered to the individual patient cumulatively at 0–12, 12–24, and 24–48 h and titration between time points at 12–24 and 24–48 h between and within centers in a large international multicenter trial of temperature targets after cardiac arrest to characterize current practices. Secondly, we aimed to investigate clinically important outcomes that might be associated with that specific analgosedation pratices. We hypothesized there would be a significant variation in the specific analgosedation practices between and within centers and that this might be associated with the time to awakening, incidence of clinical seizures, or long-term survival.

Material and Methods

Patients

The TTM trial was an international, randomized, parallel group, assessor-blinded trial designed to evaluate outcome after TTM at either 33 °C (TTM33) or 36 °C (TTM36). The inclusion criteria of the TTM trial were patients 18 years of age or older who were unconscious (a score of < 8 on the Glasgow Coma Scale) on admission to the hospital after out-of-hospital cardiac arrest of presumed cardiac cause [27]. A center was defined as a study site in the TTM trial, i.e., an ICU, and it needed to be a high-volume center with percutaneous coronary intervention availability and the ability to provide TTM. Nine hundred fifty adult patients were enrolled from November 2010 to January 2013 within 4 h of return of spontaneous circulation (ROSC) at 36 ICUs in Europe and Australia. The 36 h of intervention consisted of achievement of target temperature, maintenance of target temperature, and rewarming to 37 °C. All patients were deeply sedated, endotracheally intubated, and mechanically ventilated. Survival at 6 months and good Cerebral Performance Category (CPC), defined as CPC 1 and 2, at 6 months were used in the analysis of this study. This study had ethical approval by the Regional Ethical Review Board Lund, Protocol 2009/6 Dnr 2009/324 (TTM Trial).

Sedation and Analgesia

Approaches to sedation and analgesia were not defined in the study protocol. Centers were instructed to follow standard local practices and provide similar treatment to both intervention groups. The protocol specified that sedation should be stopped after 36 h of therapy to allow for assessment of awakening, unless required for medical reasons. Cumulative doses of sedative and analgesic drugs administered to each individual patient were collected by the treating center after primary data collection was complete [28]. This included doses of propofol, fentanyl, midazolam, morphine, remifentanil, alfentanil, sufentanil, and dexmedetomidine administered between 0 and 12 h, 12 and 24 h, and 24 and 48 h and were reported as cumulative doses of each drug type at 12, 24, and 48 h. The sedation depth may be monitored using clinical sedation assessment. The Richmond Agitation and Sedation Scale and the Critical Care Pain Observation Tool are two well-established, validated, and reliable sedation scales [29–31]. The Richmond Agitation and Sedation Scale functions by observing the patient and testing responsiveness to auditory and physical stimuli and the scale ranges from − 5 (unarousable), to 0 (alert and calm), to + 4 (combative) [29, 30]. The Critical Care Pain Observation Tool evaluates facial expression, muscle tension, movement, and compliance with ventilated breath/vocalized pain, with a total score ranging from 0 to 8 [31].

Midazolam and Fentanyl Equivalents

Sedation and analgesia were separately normalized to midazolam and fentanyl equivalents. These conversions

were based on the best available clinical and laboratory studies (see Supplement Table 1) [32–38]. Propofol was changed to midazolam equivalents and averaged over each time course and weight (in kilograms). Morphine, remifentanil, sufentanil, and alfentanil were converted to fentanyl equivalents and averaged over each time course and weight (in kilograms). Dexmedetomidine was not included, as it was only used by one site for one patient, and because there is no standard approach to conversion to midazolam equivalents.

Awakening and Clinical Seizures

Awakening was defined as the first time the patient achieved a Glasgow Coma Scale motor subscore of 6. Level of consciousness was evaluated daily by using the Glasgow Coma Scale at all sites. Inclusion day was registered as day one, and late awakening was defined as a patient being awake after day five. Neuroprognostication according to study protocol was scheduled at 72 h after rewarming (108 h after ROSC) in patients who remained unconscious with strict criteria for withdrawal of life-sustaining therapy (WLST) [39]. We analyzed the number of patients who were awake within the first 48 h. Clinical seizure is defined as myoclonic or tonic–clonic seizures at any time point during the ICU stay.

Missing Data

Only patients with sedation and analgesia data available were used in the primary analyses. To ensure the center practices are represented in the analysis for the aim of this study, we excluded centers with data for less than ten patients. We described the difference between patients with and without recorded sedation and analgesia data available by using the Wilcoxon rank-sum test, χ^2 test, and Fisher's exact test.

Analysis

Cumulative dose of each medication was calculated for all patients and summarized across all centers at each time point. Propofol was converted to midazolam equivalents in mg/kg/h and analgesics were converted to fentanyl equivalents in μg/kg/h, to be able to compare the dosing of all patients in the cohort. Continuous data are expressed as medians and interquartile ranges unless otherwise indicated.

We evaluated the number of sedative and analgesic medications using analysis of variance (ANOVA) to test for global differences between centers. To analyze the association between the use of two or more sedatives and treatment center with adjustment for baseline severity of illness, we created a multivariate model using the clinically important and design variables of the TTM trial (age, sex, witnessed arrest, shockable rhythm, time to ROSC, and shock on admission).

To adjust for baseline severity of illness, clinical factors potentially affecting the delivered dose equivalents of sedatives and analgesics were tested with a linear regression model including clinically important design variables and the target temperature of 36 °C at 12, 24, and 48 h. The center was then added to this model and the two models were compared using R^2 values and likelihood ratio testing.

Titration of sedation and analgesia was evaluated by using differences in patients' average hourly dosages between 12–24 h and 24–48 h. This was again evaluated with adjustment for baseline severity of illness using the clinically important, design variables, and the target temperature of 36 °C. The center was then added to this model and the two models were compared using likelihood ratio testing. Survival at 6 months was then added to the multivariate model to test the association of sedative and analgesia titration.

The association of sedation and analgesia dosing at 12, 24, and 48 h, on a "center" level, with late awakening and clinical seizures were evaluated using a hierarchical logistic regression model. To adjust for baseline severity of illness, clinically important and design variables of the TTM trial were added to the analyses.

The association of sedation and analgesia titration between 12–24 h and 24–48 h, on a "center" level, with late awakening and clinical seizures were evaluated using a hierarchical logistic regression model. To adjust for baseline severity of illness, clinically important, design variables of the TTM trial, and target temperature of 36 °C were added to the analyses.

Results

Among 36 centers, 21 participated in collecting sedation and analgesia data. Three centers enrolled less than ten patients and were excluded; therefore, nine patients were excluded. This left 18 centers with 614 patients to include in this study (see flowchart in Supplement Fig. 1). The proportion of patients enrolled in this study at each center ranged from 2 to 7% for 17 centers, and one center enrolled 26% of all patients. Fifteen centers out of 18 were university hospitals, and the other 3 centers were regional hospitals. One center and 163 (26%) patients were treated at a cardiac ICU and the others were treated at mixed ICUs. Most of the centers and patients (15 centers and 533 [87%] patients) used the Richmond Agitation-Sedation Scale. One center including 29 (4%) patients used Critical Care Pain Observation Tool. One center including 27 (4%) patients reported that no scale was used. One center including 29 (4%) patients did not report whether

a sedation scale was used. Patient characteristics and the frequency of sedation and analgesic used are shown in Tables 1 and 2, respectively.

A total of 325 patients from 18 centers in the TTM trial did not have sedation data or had less than ten patients at each center recorded and were not part of the cohort. These patients were less likely to have a good CPC at 180 days (Supplement Table 2).

Number of Sedatives and Analgesia Medications Used

A total of 605 (99%), 607 (99%), and 607 (99%) patients had received a sedative at 12, 24, and 48 h, respectively, whereas 519 (85%), 527 (86%), and 508 (83%) patients had received an analgesic medication at 12, 24, and 48 h, respectively. No patient received more than two sedatives or analgesic medications. We found significant differences between centers in the number of sedatives and analgesics administered for all time points ($p < 0.01$ for all using grouped testing ANOVA). This remained consistent after the model was adjusted for age, sex, time to ROSC, bystander CPR, shockable rhythm, and shock on admission ($p < 0.001$ for grouped testing using ANOVA).

Table 1 Patient characteristics

Patient characteristics	$N = 614$[a]
Age	65 (56, 72)
Female sex	113 (18%)
Arrest at home	328 (53%)
Bystander witnessed	546 (89%)
Bystander CPR	444 (72%)
Bystander defibrillation	55 (9.0%)
Shockable rhythm	498 (81%)
Number of defibrillations	2 (1, 4)
Prehospital intubation	426 (70%)
Time to ROSC (min)	25 (16, 39)
Good CPC at 6 months	303 (49%)

[a] Statistics presented: median (IQR); *n* (%)

Sedative and Analgesic Dosage

After normalizing the sedative dosages to midazolam equivalents, the median (interquartile range) dosages were 0.13 (0.08, 0.23), 0.14 (0.09, 0.24), and 0.13 (0.07, 0.22) mg/kg/h at 12, 24, and 48 h, respectively. The median (interquartile range) dosages of fentanyl equivalents were 1.21 (0.50, 2.04), 1.31 (0.52, 2.01), and 1.16 (0.49, 1.81) μg/kg/h at 12, 24, and 48 h, respectively. The dosages of fentanyl and midazolam equivalents, by center, at 12, 24, and 48 h are shown in Fig. 1. Linear models for associations with average sedative and analgesic dosages, adjusted for severity of illness and target temperature, with and without the center added to the model are shown in Table 3. Comparison of these models with likelihood ratio testing showed the center significantly improved model performance in both sedation and analgesia and at every time point ($p < 0.001$, for all models). The center effect significantly improved the R^2 values for analgesics and sedation at all time points compared with models without the center effect (see Table 3). Target temperature was not significantly associated with average dosage of sedation or analgesia at any time point in multivariate model (see Table 3).

Titration of Sedatives and Analgesics

The median difference in midazolam dosing between 12 and 24 h was 0.009 (−0.002 to 0.027) mg/kg/h and −0.015 (−0.042 to 0.001) mg/kg/h between 24 and 48 h. For fentanyl equivalents, the difference was 0.06 (−0.01 to 0.22) mg/kg/h and −0.14 (−0.40 to 0.00) mg/kg/h between 12–24 and 24–48 h, respectively. Linear models for associations with differences in sedative and analgesic dosages, adjusted for severity of illness and target temperature, with and without the center added to the model are shown in Table 4. Comparison of these models with likelihood ratio testing showed the center significantly improved the models for sedation differences between 24 and 48 h ($p < 0.001$) and for differences in fentanyl dosage between 12 and 24 h ($p = 0.04$) and 24–48 h ($p < 0.001$). The center did not significantly

Table 2 Type of sedative and analgesic drugs given within the first 12, 24, and 48 h

Medication	Proportion: 12 h *n* (%)	Dose: median (IQR)	Proportion: 24 h *n* (%)	Dose: median (IQR)	Proportion: 48 h *n* (%)	Dose: median (IQR)
Propofol (mg/kg/h)	421 (69)	2.3 (1.2, 3.8)	431 (70)	2.4 (1.4, 4.3)	432 (70)	2.2 (1.1, 3.7)
Midazolam (mg/kg/h)	244 (40)	0.07 (0.04, 0.13)	259 (42)	0.09 (0.05, 0.10)	258 (42)	0.06 (0.03, 0.10)
Fentanyl (mcg/kg/h)	304 (50)	1.7 (1.2, 2.3)	310 (50)	1.9 (1.3, 2.4)	311 (51)	1.6 (1.1, 2.1)
Morphine (mg/kg/h)	96 (16)	0.04 (0.02, 0.05)	101 (16)	0.04 (0.02, 0.05)	101 (16)	0.3 (0.01, 0.04)
Remifentanil (mcg/kg/h)	84 (14)	3.3 (2.0, 6.1)	87 (14)	3.5 (2.3, 6.4)	84 (14)	3.7 (2.7, 6.0)
Alfentanil (mcg/kg/min)	32 (5)	29.3 (22.5, 37.4)	31(5)	33.3 (28.3, 37.0)	15 (2)	27.8 (23.7, 33.2)
Sufentanil (mcg/kg/h)	16 (3)	0.2 (0.1, 0.3)	16 (3)	0.2 (0.2, 0.3)	18 (3)	0.2 (0.1, 0.2)

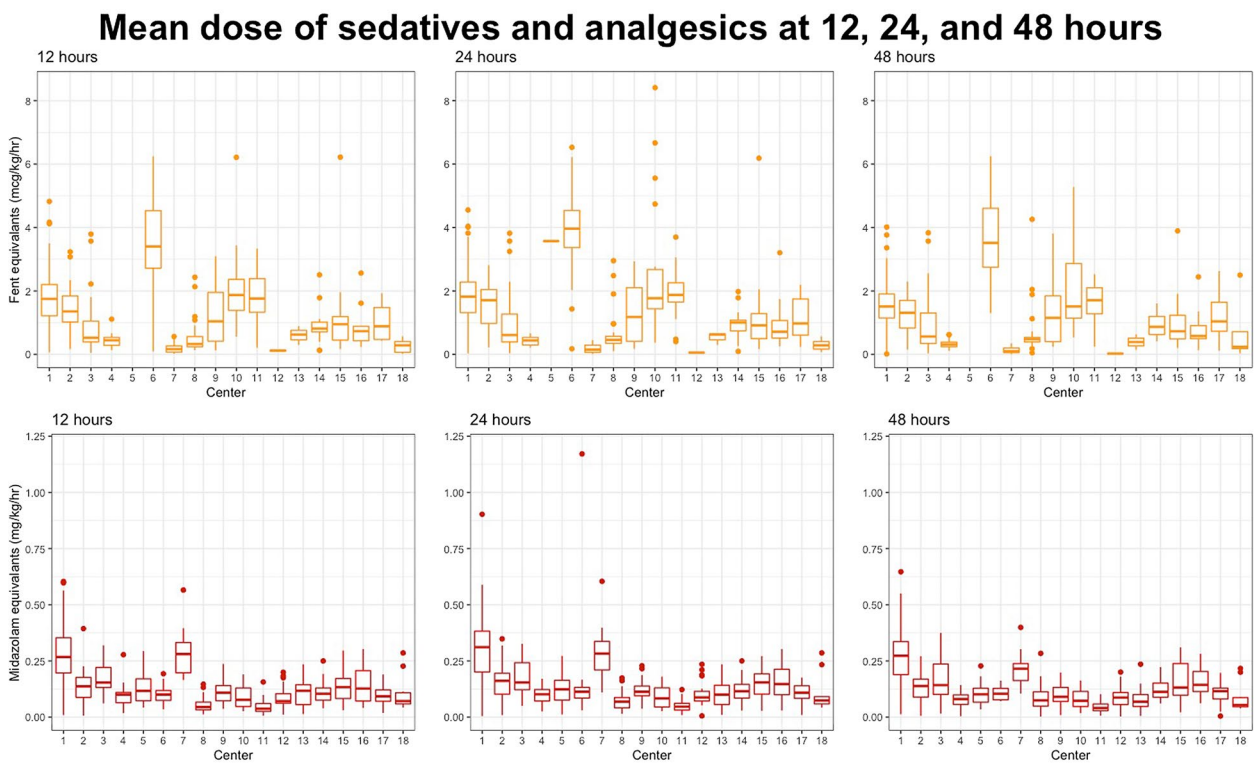

Fig. 1 Illustrating the range of average doses of fentanyl (yellow) and midazolam (red) equivalents administered to patients in each center at 12, 24, and 48 h of treatment (colour figure online)

affect the model for differences in midazolam equivalents between 12 and 24 h ($p=0.40$). When survival was added to the model, survival at 6 months was associated with decreasing dosage between 24 and 48 h for fentanyl equivalents ($p=0.048$) but not for midazolam equivalents ($p=0.75$). Decreased titration between 12 and 24 h of midazolam and fentanyl equivalents were not associated with survival at 6 months ($p=0.06$ and $p=0.38$, respectively). Target temperature was significantly associated with increased dosage of fentanyl equivalents between 12 and 24 h ($p=0.08$ and $p=0.02$, without and with center effect, respectively), but there was no significant different between 24 and 48 h (see Table 4). Target temperature was not significantly associated with titration of midazolam equivalents at any time point.

To evaluate the effect of centers by country, the centers were clustered as follows: Switzerland (two centers), Denmark (one center), Italy (three centers), Luxemburg (one center), Netherlands (two centers), Norway (one center), Sweden (three centers), and United Kingdom (five centers). We evaluated the dosing characteristics (type of medication, number of medications, average dosage) at 24 h as well as dosing differences at 12 and 24 h were largely nonsignificant, and those that were significant did not differ substantially from the cohort.

Awakening and Clinical Seizures

A total of 364 patients were alive at the end of the study period, of whom 342 had a registered day of awakening. Four patients (0.7%) the first day and 20 patients (3.3%) the second day of therapy were awake during the initial 48 h of therapy. We found a significant association of a higher average dosage of fentanyl received at 48 h with late awakening in multivariate analysis ($p=0.002$ and $p=0.003$ with and without center effect, respectively), whereas average dosage at 12 and 24 h were not significantly associated (see Supplement Table 3). Increase in titration dosing of fentanyl equivalents between 24 and 48 h was significantly associated with late awakening in multivariate analysis ($p=0.04$ and $p=0.005$ without and with center effect, respectively), shown in Supplement Table 4. Total dose of midazolam equivalents was not significantly associated with late awakening at any time point. Increased titration of midazolam equivalents between 24 and 48 h was significantly associated with late awakening in multivariate analysis ($p<0.001$ for both with and without center effect), whereas titration between 12 and 24 were not (see Supplement Table 4).

Total average dosage of midazolam equivalents at any time point was not significantly associated with clinical seizures (see Supplement Table 5). An increase in

Table 3 Association of clinical factors, target temperature and center with average doses of fentanyl and midazolam equivalents in regression model with and without center, at 12, 24, and 48 h

Patient characteristics and *R*-square values	Sedation and analgesia	12 h	12 h with center	24 h	24 h with center	48 h	48 h with center
Age[a]	Fentanyl equivalents	−0.05 ($p=0.009$)	−0.04 ($p=0.009$)	−0.07 ($p=0.003$)	−0.04 ($p=0.006$)	−0.04 ($p=0.04$)	−0.03 ($p=0.03$)
	Midazolam equivalents	−0.01 ($p=0.001$)	−0.01 ($p<0.001$)	−0.01 ($p<0.001$)	−0.01 ($p<0.001$)	−0.01 ($p<0.001$)	−0.01 ($p<0.001$)
Female sex	Fentanyl equivalents	−0.04 ($p=0.74$)	−0.12 ($p=0.22$)	−0.03 ($p=0.86$)	−0.08 ($p=0.44$)	0.02 ($p=0.84$)	−0.08 ($p=0.39$)
	Midazolam equivalents	−0.1 ($p<0.01$)	0.00 ($p=0.80$)	−0.02 ($p=0.14$)	0.00 ($p=0.83$)	−0.01 ($p=0.25$)	0.00 ($p=0.73$)
Witnessed arrest	Fentanyl equivalents	−0.06 ($p=0.71$)	0.01 ($p=0.99$)	−0.01 ($p=0.97$)	−0.03 ($p=0.81$)	0.06 ($p=0.73$)	0.05 ($p=0.69$)
	Midazolam equivalents	0.00 ($p=0.87$)	0.00 ($p=0.97$)	0.01 ($p=0.51$)	0.00 ($p=0.73$)	0.01 ($p=0.28$)	0.01 ($p=0.41$)
Shockable rhythm	Fentanyl equivalents	0.39 ($p=0.003$)	0.16 ($p=0.11$)	0.49 ($p<0.001$)	0.25 ($p=0.02$)	0.44 ($p<0.001$)	0.24 ($p=0.009$)
	Midazolam equivalents	0.02 ($p=0.05$)	0.01 ($p=0.34$)	0.03 ($p=0.01$)	0.02 ($p=0.08$)	0.03 ($p=0.007$)	0.02 ($p=0.02$)
Time to ROSC[b]	Fentanyl equivalents	−0.2 ($p=0.03$)	−0.01 ($p=0.27$)	−0.03 ($p=0.01$)	−0.01 ($p=0.21$)	−0.02 ($p=0.046$)	−0.01 ($p=0.34$)
	Midazolam equivalents	0.00 ($p<0.001$)	0.00 ($p<0.001$)	0.00 ($p<0.001$)	0.00 ($p<0.001$)	0.00 ($p<0.001$)	0.00 ($p=0.004$)
Shock onadmission	Fentanyl equivalents	0.70 ($p<0.001$)	0.35 ($p=0.006$)	0.57 ($p=0.002$)	0.23 ($p=0.10$)	0.58 ($p<0.001$)	0.27 ($p=0.03$)
	Midazolam equivalents	−0.02 ($p=0.22$)	−0.02 ($p=0.08$)	−0.01 ($p=0.65$)	−0.01 ($p=0.46$)	−0.02 ($p=0.22$)	−0.03 ($p=0.02$)
Target temperature 36 °C	Fentanyl equivalents	0.03 ($p=0.78$)	−0.08 ($p=0.26$)	0.08 ($p=0.45$)	0.00 ($p>0.99$)	0.09 ($p=0.33$)	−0.05 ($p=0.46$)
	Midazolam equivalents	−0.01 ($p=0.31$)	0.01 ($p=0.17$)	−0.01 ($p=0.59$)	−0.01 ($p=0.43$)	0.00 ($p=0.88$)	0.00 ($p=0.84$)
Center effect[c]	Fentanyl equivalents		**$p<0.001$**		**$p<0.001$**		**$p<0.001$**
	Midazolam equivalents		**$p<0.001$**		**$p<0.001$**		**$p<0.001$**
R-square values for the model	Fentanyl equivalents	0.07	0.51	0.08	0.53	0.07	0.52
	Midazolam equivalents	0.09	0.55	0.08	0.49	0.10	0.55

significant p-value with the significance level of 0.05 are in bold.

[a] Age estimate is per 5 year intervals

[b] Time to ROSC estimate is per 5 min intervals

[c] Center effect of global *p* value using ANOVA testing

titration of midazolam equivalent dosing between 24 and 48 h was significantly associated with clinical seizures ($p=0.04$), whereas titration between 12 and 24 h was not associated (see Supplement Table 6). This finding remained consistent after adjustment for clinically relevant variables, target temperature, and the center effect. Neither average dose nor titration of fentanyl equivalents during the initial 48 h of therapy were associated with clinical seizures.

Discussion

In a large randomized clinical trial population of patients receiving TTM after cardiac arrest, we found significant differences in the approach to providing sedation and analgesia. The level of target temperature was not significantly associated with total dose or titration of sedation and analgesics during the initial 48 h of therapy, except for increased titration of analgesics between 12 and 24 h with a target level of 36 °C. The treatment center was

Table 4 Association of clinical factors, center, and target temperature with difference in fentanyl and midazolam equivalent doses between 12–24 and 24–48 h with and without center

Patient characteristics	Sedation and analgesia	12–24 h difference	12–24 h difference with center	24–48 h difference	24–48 h difference with center
Age[a]	Fentanyl equivalents	0.00 ($p=0.82$)	0.00 ($p=0.72$)	0.01 ($p=0.38$)	0.00 ($p=0.56$)
	Midazolam equivalents	0.00 ($p=0.20$)	0.00 ($p=0.13$)	−3.01 ($p<0.01$)	−1.83 ($p=0.01$)
Female sex	Fentanyl equivalents	0.07 ($p=0.10$)	0.06 ($p=0.99$)	−0.01 ($p=0.88$)	−0.04 ($p=0.49$)
	Midazolam equivalents	−0.01 ($p=0.38$)	0.00 ($p=0.49$)	−0.61 ($p=0.91$)	2.09 ($p=0.65$)
Witnessed arrest	Fentanyl equivalents	0.10 ($p=0.08$)	0.10 ($p=0.09$)	0.04 ($p=0.56$)	0.05 ($p=0.47$)
	Midazolam equivalents	0.01 ($p=0.30$)	0.00 ($p=0.57$)	0.03 ($p>0.99$)	6.92 ($p=0.27$)
Shockable rhythm	Fentanyl equivalents	0.13 ($p=0.005$)	0.11 ($p=0.01$)	−0.07 ($p=0.21$)	−0.03 ($p=0.61$)
	Midazolam equivalents	0.01 ($p=0.08$)	0.01 ($p=0.13$)	13.0 ($p=0.02$)	8.23 ($p=0.08$)
Time to ROSC[b]	Fentanyl equivalents	0.00 ($p=0.38$)	0.00 ($p=0.28$)	0.01 ($p=0.30$)	0.00 ($p=0.66$)
	Midazolam equivalents	0.00 ($p=0.48$)	0.00 ($p=0.61$)	−0.30 ($p<0.01$)	0.002 ($p=0.44$)
Shock on admission	Fentanyl equivalents	−0.02 ($p=0.73$)	−0.05 ($p=0.38$)	−0.07 ($p=0.33$)	−0.01 ($p=0.89$)
	Midazolam equivalents	0.01 ($p=0.18$)	0.01 ($p=0.26$)	−7.77 ($p=0.25$)	−11.4 ($p=0.049$)
Target temperature at 36 °C	Fentanyl equivalents	**0.09 ($p=0.01$)**	**0.08 ($p=0.02$)**	−0.03 ($p=0.52$)	−0.04 ($p=0.36$)
	Midazolam equivalents	0.01 ($p=0.27$)	0.00 ($p=0.36$)	1.41 ($p=0.73$)	2.97 ($p=0.39$)
Centereffect[c]	Fentanyl equivalents		**$p=0.048$**		**$p<0.001$**
	Midazolam equivalents		$p=0.44$		**$p<0.01$**

significant p-value with the significance level of 0.05 are in bold.

[a] Age estimate is per 5 year intervals

[b] Time to ROSC estimate is per 5 min intervals

[c] Center effect of global *p* value using ANOVA testing

independently and strongly associated with the number of medications given, dosing, and titration of sedatives and analgesics, during and immediately following temperature management. Treatment center remained independently associated for most of the described parameters after adjustment for target temperature and clinically relevant variables, including markers of severity of illness like initial heart rhythm and total ischemic time. This suggests that local protocols influence sedation and analgesic dosing more than patient factors. We also found the total dose and titration of sedatives and analgesics to be associated with late awakening, clinical seizures, and survival, demonstrating the association of sedation and analgesia practices and clinically important outcomes. This study highlights the variability of sedation and analgesia practices between centers, implicating a gap of knowledge in optimal dosing and titration regimens and how this may affect the time to awakening and the incidence of clinical seizures and survival. To better determine whether the association of sedation and analgesia dosing or drug titration with clinically important outcomes is a causal one, further research in a prospective manner is needed.

We found that higher dosing at 48 h and increased dosing of analgesics between 24 and 48 h were associated with late awakening. Opioid analgesics may blunt the response to painful stimuli in the Glasgow Coma Scale and impair the pupillary light reflex, potentially affecting neurological prognostication. However, we did not find an association between average dosage of sedatives and time to awakening, which may be because most patients received a short-acting sedative (propofol 70%). These findings are in concordance with current guidelines, which advise the use of short-acting drugs (propofol, sufentanil, remifentanil) to shorten time to awakening and facilitate neurological prognostication [1]. The use of short-acting agents compared with long-acting agents (midazolam and fentanyl) has been associated with shorter duration of mechanical ventilation and earlier awakening, although no conclusion can be stated about impact on survival or neurological outcome [40–42]. Longer time to awakening makes patients susceptible to a perception of poor neurological prognosis and a premature withdrawal of life-sustaining therapies that can affect the ultimate outcome [43]. Further investigations of the effects of sedation and analgesics on neurological prognostication and outcome are warranted.

The need to control shivering in patients receiving TTM is important, regardless of the target temperature, and either escalation of sedation dosing or the use of NMB with a basal sedation dose is typically used to achieve this. It is required that adequate sedation

is provided to all patients receiving NMB, as it is paramount for patient comfort. The incidence of shivering, and therefore NMB need, is related to the severity of brain injury, and escalating sedation dosing may be a reflection of attempts to control shivering. There were a small number of patients in our cohort who received no sedation. It is unclear whether these patients had severe brain injury and therefore did not require NMB or if they inappropriately received NMB without sedation. Although this information was not available in our data, the incidence, severity, and response to shivering should be closely evaluated to understand the effects of sedation dosing and titration.

Sedatives are antiepileptic and frequently used as treatment for clinical seizures during TTM; we speculate this may explain the association found in this study between increased sedative dosing between 24 and 48 h and clinical seizures [44–48]. We also found decreased dosing of analgesics to be associated with improved survival. Sedation and analgesia were mandatory during TTM for 36 h, and thus the dosing collected at 48 h reflect the dosing in patients with prolonged sedation. Prolonged sedation and analgesia may relate to increased shivering, which is associated with good outcome after cardiac arrest, but also pose a risk of secondary brain injury if not properly treated [49]. However, prolonged sedation and analgesia may also be due to patients having frequent myoclonus, indicating more severe brain injury and the need for continued sedation and analgesia [45]. Another common reason for prolonged sedation is the need for continued mechanical ventilation. These are possible reasons for the association found between dosing and titration with late awakening, the prevalence of clinical seizures and survival. Although sedatives may affect cerebral oxygen consumption, cerebral blood flow, and can suppress seizures, it remains unclear if sedation provides additional neuroprotective effects during TTM [3, 4, 17]. We speculate that the optimal dosage of sedatives needed during the post cardiac arrest care might depend on the severity of brain injury. Thus, sedation dosing should be individualized to the patient's severity of brain injury, presence of myoclonus and shivering, and the intensity of shivering. These methods could be refined as future studies provide more information regarding phenotyping or better accounting for heterogeneity in this population.

The "center effect" is highlighted most prominently in analyzing the dosage of analgesia and sedatives. Here, the model without centers performed relatively poorly, with clinical factors accounting for only 7–10% of the variability of dosing differences (reflected in the *R*-squared). When "center" was added, the model was able to account for roughly half of the variability. Clearly, the dosing for these patients is complicated and there is still much work to be done to determine how bedside sedation decisions are being made. However, evaluation of single-center influence of sedation dosing, without the use of other physiologic end points, is of little use. It should be acknowledged that participating centers were high-volume cardiac arrest centers treating patients in the setting of a randomized trial. It is unknown if there would be similar findings in a "real world" setting across lower-volume institutions and outside of clinical trials. This variability should be further studied in larger cohorts that are powered to risk adjust for patient severity of illness to determine whether there is an individual effect on outcome for sedation and analgesia dosing on individual patients. Understanding this effect would inform trials to determine a synchronized approach to individualizing sedation and analgesia dosing.

A limitation of this study is that the primary objective of the TTM trial was not to investigate sedation and analgesia management, and thus dosing data were collected retrospectively. As such, not all centers participated, and data were collected up to 48 h although the trial intervention ended at 36 h. There were 623 out of 939 patients from the main trial with complete sedation and analgesia data, which may have introduced responder bias. We found a significantly lower rate of good CPC outcome, 42% compared with 49%, in patients without sedation data. This finding is a possible site effect because not all centers from the main TTM trial participated in this study. This study reports data collected more than 10 years ago from the TTM trial, another potential limitation of this study. However, this study is the first of our knowledge reporting individual patient sedation and analgesia data across several centers and these medications are still used in current practices. Postcardiac arrest organ dysfunction, specifically liver and kidney, may impact clearance of sedative and analgesic drugs and we not adjusted for, representing a limitation of this study. Although this is the largest study to evaluate the effects of sedation on outcomes after cardiac arrest, several limitation warrant discussions. As discussed above, the use of NMB and presence of shivering were not collected for this study. Given that sedation is required for patients receiving NMB, variation in the use of NMB and presence of shivering may have impacted the dosing and titration of sedatives and the relation to outcome. However, this may not only vary between centers but also between patients within centers depending on the severity of brain injury. Thus, the reasons for dosing and titration decisions were not available and should be further studied in a prospective manner to better understand the nuance of these differences. We also cannot determine causation in a retrospective study, so the associations we noted between sedation and analgesia dosing and titration with

delayed awakening and clinical seizures at various time points should be considered as hypothesis-generated rather than definitive. The occurrence of subclinical seizures that may impact the sedation and analgesia dosing were not captured in this study, which is a limitation.

Conclusions

We identified significant differences between centers in the choice of sedative and analgesic drugs, specific drug dosing, and titration during and immediately following TTM after out-of-hospital cardiac arrest. Higher dosages and upward titration of analgesics and sedatives during the initial 48 h of therapy were associated with delayed awakening and a higher incidence of clinical seizures. We also found that a downward titration of analgesics was significantly associated with survival at 6 months. The present study cannot assess the causal relation of the associations reported, and thus the findings are to be interpreted with caution. Clinical prospective trials comparing different regimens of sedations are needed to further elucidate these findings.

Supplementary Information

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Author details

[1] Division of Anesthesia and Intensive Care, Department of Clinical Sciences Lund, Helsingborg Hospital, Lund University, Svartbrödragränden 3, 251 87 Helsingborg, Sweden. [2] Department of Critical Care, Maine Medical Center, Portland, ME, USA. [3] Division of Anesthesia and Intensive Care, Department of Clinical Sciences Lund, Skane University Hospital, Lund University, Lund, Sweden. [4] Division of Neurology, Department of Clinical Sciences, Skane University Hospital, Lund University, Lund, Sweden. [5] Department of Cardiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark. [6] Division of Anesthesia and Intensive Care, Department of Clinical Sciences Lund, Skane University Hospital, Lund University, Malmö, Sweden. [7] Division of Cardiology, Department of Clinical Sciences Lund, Skane University Hospital, Lund University, Lund, Sweden.

Author Contributions

Drs AC, TLM, AL, TC, and NN contributed to study concept and design. AL, JD, CH, and JK contributed to data acquisition. AC and TLM contributed to analyses and interpretation of data. AC, TLM, AL, TC, DBS, RRR, CH, JK, ZH, HF, JD, and NN contributed to drafting the article. The authors have read and approved of the final manuscript.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical Approval/Informed Consent

This study had ethical approval by Regional Ethical Review Board Lund, Protocol 2009/6 Dnr 2009/324 (targeted temperature management trial).

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Clinical paper

Hypothermia versus normothermia after out-of-hospital cardiac arrest; the effect on post-intervention serum concentrations of sedatives and analgesics and time to awakening

Martin Annborn[a], *Ameldina Ceric*[b,*], *Ola Borgquist*[c], *Joachim During*[b], *Marion Moseby-Knappe*[d], *Anna Lybeck*[c]

Abstract

Background: This study investigated the association of two levels of targeted temperature management (TTM) after out-of-hospital cardiac arrest (OHCA) with administered doses of sedative and analgesic drugs, serum concentrations, and the effect on time to awakening.

Methods: This substudy of the TTM2-trial was conducted at three centers in Sweden, with patients randomized to either hypothermia or normothermia. Deep sedation was mandatory during the 40-hour intervention. Blood samples were collected at the end of TTM and end of protocolized fever prevention (72 hours). Samples were analysed for concentrations of propofol, midazolam, clonidine, dexmedetomidine, morphine, oxycodone, ketamine and esketamine. Cumulative doses of administered sedative and analgesic drugs were recorded.

Results: Seventy-one patients were alive at 40 hours and had received the TTM-intervention according to protocol. 33 patients were treated at hypothermia and 38 at normothermia. There were no differences between cumulative doses and concentration and of sedatives/analgesics between the intervention groups at any timepoint. Time until awakening was 53 hours in the hypothermia group compared to 46 hours in the normothermia group ($p = 0.09$).

Conclusion: This study of OHCA patients treated at normothermia versus hypothermia found no significant differences in dosing or concentration of sedatives or analgesic drugs in blood samples drawn at the end of the TTM intervention, or at end of protocolized fever prevention, nor the time to awakening.

Keywords: Cardiac arrest, Targeted temperature management, Sedation, Awakening, Serum concentration, Propofol, Midazolam

Background

Many patients remain comatose and require mechanical ventilation in the intensive care unit (ICU) after resuscitation from cardiac arrest. Targeted temperature management (TTM) at 32–34 °C for 24–48 hours was established as a neuroprotective strategy in unconscious survivors of cardiac arrest in 2002.[1,2] Deep sedation was introduced as an essential part of the TTM regimen to counteract undesirable physiological effects and discomfort from induced hypothermia, and to facilitate the cooling process. Current European guidelines recommend TTM at <37.8 °C (targeted normothermia) for 72 hours in comatose patients but make no comments on use of sedation, or duration apart from suggesting short acting sedatives.[3,4]

In a post-hoc analysis of the TTM-trial we found that time until awakening was longer in patients managed at 33 °C compared to

Abbreviations: AED, Antiepileptic drug, BSAS, Bedside shivering and assessment scale, BMI, Body Mass Index, EDTA, Ethylenediamine tetra acetic acid, ICU, Intensive care unit, FOUR score, Full outline of unresponsiveness score, NSE, Neuron-specific enolase, GFR, Glomerular filtration rate, TTM, Targeted temperature management, RASS, Richmond Agitation Sedation Scale

* Corresponding author at: Lund University, Department of Clinical Sciences Lund, Anesthesia and Intensive Care, Skane University Hospital, Carl Bertil Laurels gata 9, 214 28 Malmo, Sweden.

E-mail address: ameldina.ceric@med.lu.se (A. Ceric).

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36 °C despite administration of similar doses of sedative and analgesic drugs, and with the same degree of neurological injury in both groups.[5] Drug metabolism is slower and more variable in the critically ill as compared to healthy volunteers and hypothermia decreases drug elimination with an increased risk of lingering effects of sedation.[6–9] Effects of sedative and analgesic drugs may confound both clinical neurological examination and neurophysiological investigations employed in neurological prognostication with consequences on decisions on withdrawal of life support (WLST).[3] Serum concentrations of sedatives during post cardiac arrest care have previously only been studied in a 14-patient cohort managed at hypothermia compared with eight matched critically ill normothermic, non-cardiac arrest patients.[10,11]

The aim of this study was to investigate the association of two levels of targeted temperature management after out-of-hospital cardiac arrest (OHCA) with 1) Administered cumulative doses of sedative and analgesic drugs; 2) Serum concentrations of these drugs; 3) The effect on time to awakening. Our hypothesis was that higher serum concentrations of sedative and analgesic drugs could explain delayed awakening in patient managed at 33 °C.

Methods

Study-population

This study was performed at three hospitals in southern Sweden 2018–2020 as a substudy of the TTM2-trial, ClinicalTrials.gov number, NCT02908308, registered September 20, 201.[12,13] The TTM2-trial randomised 1900 unconscious survivors of OHCA of presumed cardiac cause to targeted hypothermia at 33 °C or targeted normothermia at <37.8 °C with mandatory deep sedation for 40 hours. Inclusion and exclusion criteria for the TTM2-trial have been described previously.[12] Additional exclusion criteria for this substudy were patients with discontinued TTM or death during the intervention.

Ethics approval and consent to participate

This study was approved by Regional Ethical Review Board in Lund, Sweden (Nr 2015/228 and 2017/36) and was carried out in accordance with the World Medical Association's Declaration of Helsinki. Written informed consent was waived, deferred, or obtained from a legal surrogate, depending on the circumstances, and was obtained from each patient who regained mental capacity.

Patient management

Apart from the temperature intervention, patient management was the same in both treatment groups. The three study sites employed a common local study-protocol based on the trial protocol.[14] Hypothermia was maintained for 28 hours, followed by rewarming to 37 °C for 12 hours (1/3°C/hour), leading to a total duration of the intervention phase of 40 hours. Deep sedation, Richmond Agitation and Sedation Scale (RASS) −4/-5 was mandatory in both patients' groups throughout the intervention phase. Short-acting drugs, i.e. propofol and remifentanil, were recommended.[15] After the intervention period, sedation was discontinued or tapered according to clinical state. Extubation was attempted at earliest time possible, based on standard protocols for discontinuation of mechanical ventilation. After the 40-hour intervention phase, a target temperature management below 37.8 °C was maintained until 72 hours in patients who remained unconscious. Consciousness was defined as Full Outline of Responsiveness Score (FOURScore) motor component of four (obeying commands). Multimodal neurological prognostication was performed at no earlier than 96 hours with strict criteria for WLST according to the TTM2-trial study protocol.[12]

Shivering was assessed using the bedside shivering assessment scale (BSAS) which ranges from zero (no shivering) to three (severe shivering). The goal was to maintain BSAS 0–1.[16] All patients received prophylactic acetaminophen/paracetamol. Shivering was treated according to local protocol, which advised increased sedation, magnesium clonidine and neuromuscular blocking drugs at the discretion of the treating physician.

Local protocol stated that all epileptic seizures, whether clinical and/or electrographic, mandated treatment with an antiepileptic drug (AED). Hence, the time (day and hour) of initiated treatment with antiepileptic medication was registered and used as marker of epileptic seizure activity in this study. First choice of drug was valproic acid or levetiracetam while second line drugs included phenytoin, fosphenytoin, diazepam, clonazepam, lorazepam, topiramate, phenobarbital, or lacosamide at the discretion of the treating physician.

Poor long-term functional outcome was defined as modified Rankin-scale (mRS) score 4–6 (moderately severe disability, severe disability, and death) at six months after cardiac arrest.[17]

Sedative and analgesic drugs

Cumulative dosing of each sedative and analgesic drug administered 0–40 (end of intervention) and 40–72 (end of targeted normothermia) hours after randomization were recorded. The types of drugs collected were midazolam (mg), propofol (mg), dexmedetomidine (mcg), clonidine (mcg), esketamine (mg), ketamine (mg), fentanyl (mcg), morphine (mg), remifentanil (mcg) and oxycodone (mg). The time of discontinuation of sedation (day, hour, and minutes) and time of awakening (day, hour, and minutes) were registered.

Blood samples

Blood samples were drawn in vials with ethylenediaminetetraacetic acid (EDTA). Samples were collected at 40 (end of intervention) and 72 hours (end of targeted normothermia) after randomization and sent to hospital laboratory services, centrifugated, and frozen to −20 °C. Analyses were performed at the Department of Forensic Chemistry, The National Board of Forensic Medicine, University of Linköping, Sweden. To ensure stability of substances, samples were sent for analysis every fourth months. The liquid chromatography-tandem mass spectrometry (LC-MS/MS) method, a validated and applied to critically ill patients, was used for quantification of clonidine, dexmedetomidine, fentanyl, ketamine, ketobemidone, midazolam, morphine and oxycodone in blood samples, while oxycodone was analyzed using chromatography–mass spectrometry (GC–MS).[18] Limits of quantifications were 0.005 mcg/ml and 0.05 mcg/ml, for oxycodone and propofol, respectively. Remifentanil was not included in the analysis due to rapid metabolism in plasma.

Statistical analyses

Continuous data are presented as median and interquartile range (IQR) and significance test using Wilcoxon rank sum test or Wilcoxon rank rum exact test. Categorical variable reported using percentages and significance was tested using Pearson's Chi-square test. The probability of awakening from the time of discontinued sedation until 180 days after randomization was analyzed using Kaplan-Meier estimates and log rank test was performed, sensitivity analyses was performed in subgroups of patients treated with midazolam and without

midazolam, to analyze the effect of long-acting sedative drugs compared to short-acting. The association of the concentration of propofol at 40 and 72 hours respectively, with the level of targeted temperature management were evaluated in a linear regression model. Age, sex, body mass index (BMI), peak neuron specific enolase, peak bilirubin, and dose of propofol at 40 and 72 hours respectively, were added to the models to adjust for severity of illness. The association of shivering and seizures with dose of propofol at 40 and 72 hours respectively, was assessed by linear regression. Differences in doses of midazolam at 40 and 72 hours between patients with and without seizures were analyzed using Wilcoxon rank sum test.

Results

Eighty-six patients were eligible for inclusion in this study. Fifteen patients were excluded due to death within 40 hours after randomization or discontinued TTM, leaving 71 patients to be included in this study (Supplemental Fig. 1). 33/71 patients (46%) were randomized to hypothermia treatment. Patients and background characteristics are shown in Table 1. The groups were similar regarding BMI, peak bilirubin, lowest reported glomerular filtration rate (GFR) on day 1–4 or peak neuron specific enolase (NSE) at 24–72 hours, time to awakening, time to extubation, length of ICU-stay and poor functional outcome at 6 months (Table 2).

Administered doses and serum concentrations of sedative and analgesic drugs

Cumulative median doses of sedatives and analgesic drugs in the two levels of TTM are shown in Table 3.

Propofol was administered in 62 (87%) patients at 0–40 hours and in 55 (77%) at 40–72 hours and remifentanil was administered in 62 (87%) patients at 0–40 hours and 53 (75%) at 40–72 hours. The median serum concentration of propofol in the hypothermia group was 1.80 (IQR 1.30, 2.30) and 0.96 (IQR 0.40, 1.63) mcg/ml at 40 and 72 hours, respectively, and in the normothermia group 1.60 (IQR 0.95, 2.30) and 0.51 (IQR 0.21, 1.23) mcg/ml at 40 and 72 hours, respectively (Table 4, Fig. 1). Median concentrations of sedatives and analgesics at 40 and 72 hours for the two levels of TTM are shown in Table 4. There were no statistically significant differences in median concentration of propofol at 40 hours, $p = 0.2$, or 72 hours, $p = 0.10$ (Table 4).

Time until awakening

In the hypothermia group, 19/33 (58 %) patients regained consciousness compared to 25/38 (66 %) patients in the normothermia group. Median time to awakening was 53 hours (IQR 45, 108) and 46 hours (IQR 41, 52) for hypothermia and normothermia respectively ($p = 0.09$). The time from when sedation was stopped to awakening was similar in the two groups, $p = 0.1$ (Fig. 2). Separate analyses were performed for patients who received midazolam and those who did not receive midazolam (Supplementary Figs. 2 and 3). No difference was detected between TTM groups in time from sedation was discontinued to awakening, in patients who did not receive midazolam ($p = 0.6$). Among the small number of patients who received midazolam and awoke, the time until awakening was statistically significantly longer in those managed at hypothermia (n = 3, median 7.0 hours IQR −2.5–11.4) compared to those managed at normothermia (n = 5, median 1 hours IQR 0.6–1.0, $p = 0.03$).

Seizures and shivering

Shivering was more common in the hypothermia group, ($p = 0.003$). Presence of shivering was associated with the cumulative propofol dose at 40 ($p = 0.006$) but not at 40–72 hours (Supplemental Table 1). Antiepileptic drugs were more commonly administered in the hypothermia group, ($p = 0.015$), but time to first AED administration was similar in both intervention groups (Table 2). Administration of AED, as a marker of seizures, was not associated with doses of propofol at 0–40 or 40–72 hours (Supplemental Table 1). Doses of midazolam in patients with or without seizures and shivering are shown in Supplemental Table 2.

Predictors of serum concentrations of propofol

The level of TTM was not significantly associated with concentration of propofol at 40 hours in univariable analyses ($p = 0.74$) or at 72

Table 1 – Patient and background characteristics.

Characteristic	Hypothermia, N = 33	Normothermia, N = 38
Age, Median (IQR)	66 (57, 74)	66 (60, 74)
Female, No. (%)	8 (24%)	10 (26%)
Frailty score, Median (IQR)	3 (2, 3)	3 (2, 4)
BMI, Median (IQR)	25.3 (23.3, 28.4)	26.2 (23.9, 28.3)
Previous renal disease, No. (%)	0 (0%)	0 (0%)
Previous liver disease, No. (%)	0 (0%)	0 (0%)
Witnessed arrest, No. (%)	29 (88%)	37 (97%)
Bystandard CPR, No. (%)	24 (73%)	30 (79%)
Initial shockable rythm, No. (%)	21 (64%)	29 (76%)
Circulatory shock on admission, No. (%)	8 (24%)	12 (32%)
Time to ROSC (min), Median (IQR)	32 (20, 40)	24 (16, 36)
FOUR motor score on admission, Median (IQR)	0 (0, 1)	0 (0, 2)
Bilateral corneal reflexes present on admission, No. (%)	8 (53%)	14 (64%)
Bilateral pupillary reflexes present on admission, No. (%)	17 (59%)	24 (69%)

BMI = Body mass index; CPR = Cardiopulmonary resuscitation; ROSC = Return of spontaneous circulation; FOUR = Full outline of unresponsivness. Shock at admission was defined as a systolic blood pressure of less than 90 mm Hg for more than 30 minutes or end-organ hypoperfusion (cool arms and legs, urine output <30 ml per hour, and heart rate <60 beats per minute).

Table 2 – ICU variables and outcomes.

Characteristic	Hypothermia, N = 33	Normothermia, N = 38	p-value[1]
Shivering, No. (%)	23 (70%)	13 (34%)	0.003
Antiepileptic drug, No. (%)	16 (48%)	8 (21%)	0.015
Time to AED start, Median (IQR)	38 (20, 45)	34 (20, 50)	0.9
Highest NSE, Median (IQR)	42 (29, 94)	28 (21, 76)	0.068
Highest bilirubin day 1–4, Median (IQR)	14 (9, 22)	12 (8, 16)	0.4
Lowest GFR day 1–4 (ml/min/1,73 m^2), Median (IQR)	58 (49, 68)	58 (35, 72)	0.6
Time to extubation (days), Median (IQR)	3.5 (2.0, 4.7)	2.9 (1.9, 4.5)	0.3
Time to awakening (hours), Median (IQR)	53 (45, 106)	46 (41, 52)	0.090
ICU length of stay (days) in patients alive at discharge, Median (IQR)	3.2 (2.6, 6.9)	3.2 (2.7, 5.9)	>0.9
Good neurological outcome at 6 months (mRS 1–3), No. (%)	16 (48%)	19 (50%)	0.9

AED = Antiepileptic drug; NSE = Neuron specific enolase; GFR = Glomerular filtration rate; ICU = Intensive care unit; mRS = Modified Rankin scale.

[1] Pearson's Chi-squared test; Wilcoxon rank sum exact test; Wilcoxon rank sum test.

Table 3 – Total cumulative doses of sedatives and analgesics at 40 and 72 hours.

Drug	Hypothermia, N = 33[1]	N	Normothermia, N = 38[1]	N	p-value[2]
Propofol at 0–40 hrs (mg)	8,020 (6,600, 9,706)	29	7,700 (5,384, 10,000)	33	0.7
Midazolam at 0–40 hrs (mg)	18 (10, 33)	8	55 (22, 106)	5	
Clonidine at 0–40 hrs (mcg)	90 (90, 90)	1	1,050 (1,020, 1,080)	2	
Esketamine at 0–40 hrs (mg)	NA	0	905 (905, 905)	1	
Remifentanil at 0–40 hrs (mcg)	18,100 (12,750, 23,505)	29	19,345 (12,700, 31,800)	33	0.5
Fentanyl at 0–40 hrs (mcg)	100 (100, 1,782)	3	225 (150, 250)	4	
Oxicodone at 0–40 hrs (mg)	12 (4, 19)	4	25 (22, 58)	3	
Propofol at 40–72 hrs (mg)	3,339 (1,745, 5,790)	26	2,140 (854, 5,516)	29	0.3
Midazolam at 40–72 hrs (mg)	6 (2, 16)	5	11 (10, 68)	3	
Clonidine at 40–72 hrs (mcg)	NA (NA, NA)	0	150 (94, 267)	3	
Esketamine at 40–72 hrs (mg)	25 (25, 25)	1	NA (NA, NA)	0	
Dexmetomidon at 40–72 hrs (mcg)	2,216 (2,216, 2,216)	1	160 (120, 308)	3	
Remifentanil at 40–72 hrs (mcg)	8,650 (3,275, 14,775)	24	6,765 (2,765, 13,400)	29	0.6
Fentanyl at 40–72 hrs (mcg)	300 (300, 300)	1	100 (50, 150)	2	
Oxicodone at 40–72 hrs (mg)	9 (6, 23)	7	10 (4, 25)	10	
Morphine at 40–72 hrs (mg)	NA	0	10 (8, 13)	2	

No patients received ketamine at any timepoint. No patients received dexmetomidon or morphine at 0–40 hrs.

P-values were not analyzed for variables with few patients.

[1] Data presented as median (IQR) for all variables.

[2] Wilcoxon rank sum exact test; Wilcoxon rank sum test.

Table 4 – Serum concentration of sedatives and analgesics.

Drugs	Hypothermia, N = 34[1]	N	Normothermia, N = 37[1]	N	p-value[2]
Propofol at 40 hrs (mcg/g)	1.80 (1.30, 2.30)	33	1.60 (0.95, 2.30)	31	0.2
Midazolam at 40 hrs (mcg/g)	0.07 (0.03, 0.27)	7	0.12 (0.05, 0.33)	5	
Clonidine at 40 hrs (mcg/g)	NA (NA, NA)	0	0.0030 (0.0014, 0.0048)	4	
Ketamine at 40 hrs (mcg/g)	NA (NA, NA)	0	0.3800 (0.3800, 0.3800)	1	
Fentanyl at 40 hrs (ng/g)	0.07 (0.06, 0.09)	8	0.08 (0.06, 0.11)	5	
Oxicodone at 40 hrs (mcg/g)	NA (NA, NA)	0	0.1400 (0.1400, 0.1400)	1	
Propofol at 72 hrs (mcg/g)	0.96 (0.40, 1.63)	24	0.51 (0.21, 1.23)	30	0.10
Midazolam at 72 hrs (mcg/g)	0.03 (0.02, 0.04)	5	0.07 (0.04, 0.16)	6	
Clonidine at 72 hrs (mcg/g)	0.0022 (0.0014, 0.0024)	3	0.0023 (0.0020, 0.0026)	4	
Fentanyl at 72 hrs (ng/g)	0.13 (0.10, 0.27)	4	0.07 (0.06, 0.08)	2	
Oxicodone at 72 hrs (mcg/g)	0.015 (0.010, 0.025)	8	0.013 (0.011, 0.020)	11	
Morphine at 72 hrs mcg/g)	NA (NA, NA)	0	0.12 (0.09, 0.16)	2	

No reported concentration of ketobemidon at any timepoint. No reported concentration of dexmedetodomidin or morphine at 40. No reported concentration of dexmedetomidin or ketamine at 72 hrs.

[1] Data presented as median (IQR) for all variables.

[2] Wilcoxon rank sum test; Wilcoxon rank sum exact test.

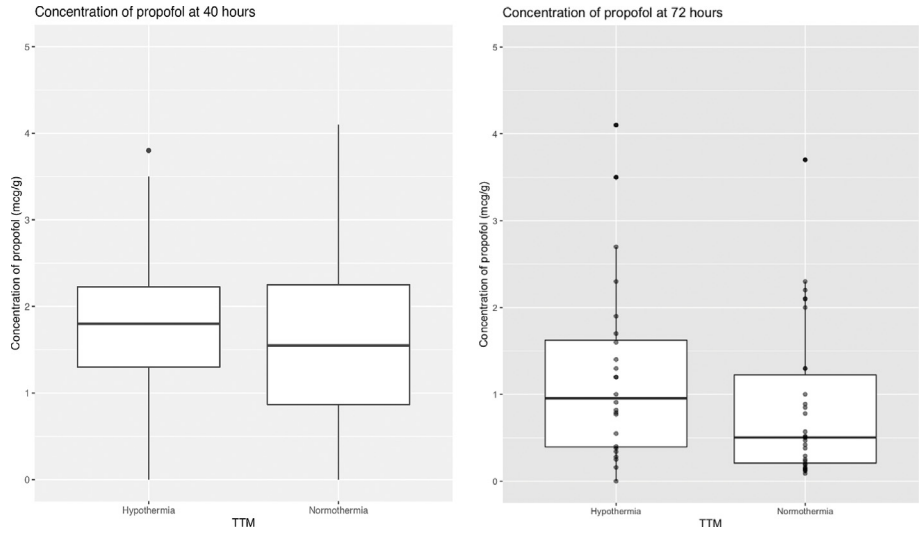

Fig. 1 – Boxplots of serum concentrations of propofol at 40 and 72 hours. Legend: Median serum concentrations of propofol at 40 hours were 1.80 (1.30, 2.30) in hypothermia patients compared to 1.60 (0.95, 2.30) normothermia patients, p = 0.2. Median serum concentrations of propofol at 72 hours were 0.96 (0.40, 1.63) in hypothermia patients compared to 0.51 (0.21, 1.23) in normothermia patients, p = 0.10. Two outliers not shown in the figure with concentration of 6,9 mcg/g (hypothermia) and 24,0 mcg/g (normothermia) at 40 hours.

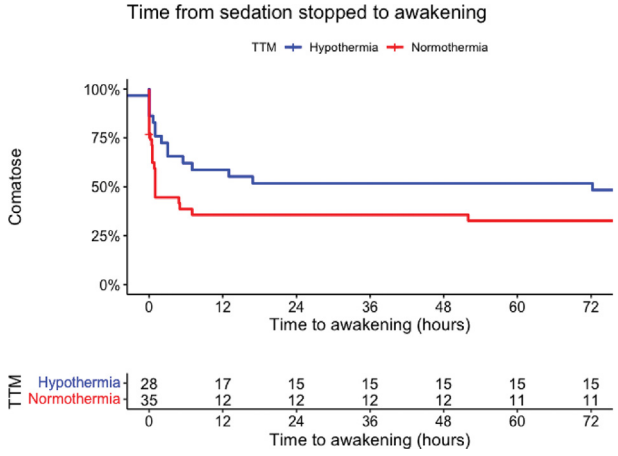

Fig. 2 – Time from sedation stopped to awakening in patients receiving propofol and midazolam. Legend: The time from sedation discontinued to awakening was analyzed using log rank test and showed no significant difference in time to awakening between normothermia and hypothermia groups, p = 0.1.

hours (p = 0.49) (Supplemental Table 3). In multivariable linear regression analysis of potential predictors of serum concentrations of propofol (age, sex, BMI, peak NSE, highest bilirubin and doses of propofol) at 40 and 72 hours, TTM was not significantly associated at either 40 ($p > 0.9$) or 72 hours ($p = 0.12$) (Supplemental Table 4). BMI was the only variable associated with serum concentrations of propofol at 40 hours, p = 0.023. Age, p = 0.05, and administered dose of propofol at 40–72 hours, p = 0.008, was associated with propofol concentrations at 72 hours (Supplemental Table 5).

Discussion

This multicenter trial is, to our knowledge, the largest study on serum concentrations of sedative drugs during post cardiac arrest care. The majority of patients received short acting drugs. We found no statistically significant differences in administered doses or serum concentration of sedatives or analgesics at any of the investigated timepoints between patients managed at hypothermia or normothermia. In a multivariate analysis correcting for other confounders, temperature was not a predictor of serum concentrations of propofol. However, the median administered doses of propofol were more than 50% higher between 40–72 hours and median serum concentrations for propofol were nearly twice as high 72 hours in the hypothermia group compared to the normothermia group. There was no statistically significant differences in time to awakening after discontinuation of sedative drugs between normothermia and hypothermia. The small subgroup of patients sedated with midazolam had statistically significantly longer time to awakening if managed at hypothermia but the number of patients was very small.

Critical illness and lower body temperature slow the metabolism and clearance of sedative drugs, an effect mediated by lowered hepatic blood flow and effects on the cytochrome P450 system.[6,7,10,19–22] There was a tendency towards higher doses and serum concentrations of propofol was observed in patients managed at hypothermia but the level of TTM was not significantly associated with serum concentration when corrected for confounders. In a smaller study on pharmacokinetics of sedative and opioid analgesic drugs during TTM for postcardiac arrest care, Bjelland et al found lower clearance of propofol, fentanyl and morphine but not midazolam compared to a control group of normothermic general ICU patients.[10] Another study on post cardiac arrest patients undergoing hypothermia, serum concentrations of remifentanil, propofol, and midazolam decreased with rewarming (when adjusting for infusion rates)

whereas fentanyl concentrations did not.[11] Results on pharmacokinetics of sedatives during post cardiac arrest care and TTM are based on small patient cohorts and firm conclusions cannot be drawn. Regardless of level of TTM, lingering effects of sedation must be considered when interpreting clinical examination and neurophysiological tests used for neuroprognostication and decisions on WLST.

Previous studies have reported longer times until awakening in patients managed at hypothermia.[5,23,24] In this study, a trend towards longer times from cardiac arrest until to awakening was observed in patients managed at hypothermia. In the small subset of patients receiving midazolam, the time until awakening was significantly longer in the hypothermia group. Elimination of propofol is faster than midazolam and it is possible that the delayed awakening was due to lingering effects of midazolam. Renal function was similar in the two patient groups but effects of individual patient factors such as degree of brain injury and rates of drug metabolism cannot be excluded. However, as the number of patients who received midazolam was small conclusions are limited.

The TTM2-trial reported cumulative drug doses at 0–72 hours.[12] Reported doses of propofol, midazolam, and remifentanil were similar to those reported in the present substudy of the TTM2-trial, suggesting generalizability of our results.[12] Reported propofol doses in this study are also similar to those reported at 0–48 hours in a substudy of the TTM-trial.[5] Remifentanil was used in higher doses in the TTM2-trial than the TTM-trial, also suggesting a change in clinical practice towards shorter-acting drugs. A single-center study on delirium after postcardiac arrest care with TTM reported higher doses of sedatives in patients managed at TTM33°C than TTM36°C, but doses differed from those in our study.[25] The effect of sedative drugs will depend on the concentration at the effector site (brain) as well as patient factors including neurological state.

Dosing of sedative agents may be affected by several clinical variables, including dosing of analgesics, shivering and seizures. In our cohort there were no differences in doses or serum concentrations of analgesics between treatment groups, suggesting this was not an important confounder in the present study.[26–28] Shivering is common during TTM and is treated due to the associated increased metabolic rate and oxygen consumption that may exacerbate secondary brain injury.[16,29] We found a significantly higher prevalence of shivering in the hypothermia group compared to the normothermia group ($p = 0.003$), consistent with previously published data from the TTM2-trial.[12] The presence of shivering was associated with administered dose of propofol at 0–40 hours (i.e., during the TTM intervention - which is in accordance with the local protocol for treatment of shivering) but not at 40–72 hours. Thus, shivering may be a potential reason for increased dosing of sedatives in our study. Seizures are associated with poor neurological outcome after cardiac arrest and may be treated with sedatives and antiepileptic agents.[30] This study used treatment with an antiepileptic drug as a marker for any type of seizure (clinical or electrographic). Using this marker, we found a higher incidence of seizures in the hypothermia group compared to the normothermia group ($p = 0.015$). Seizures were not associated with doses of propofol or midazolam which suggests adequate treatment effect of antiepileptic drugs without need for increased sedation. The higher incidence of seizures in the hypothermia group may reflect a more severe brain injury in this treatment group, as NSE levels were somewhat higher, $p = 0.068$. Despite the possible difference in neurological injury, there were no differences in doses or serum concentrations of sedatives or time until awakening (excluding patients who received midazolam) between patients managed at hypothermia or at normothermia. This suggests that seizures were not a significant confounder in this study. An alternative explanation is that the lower doses of sedatives required to reach a state of deep sedation in more severe brain injury may have cancelled increased dosing due to seizures.

Limitations

The study is strengthened by use of data from multiple study-sites in the setting of a randomized trial, and patients managed according to a protocol with similar management between sites, apart from the TTM-intervention. However, this study has several limitations. Most patients received short acting drugs, limiting conclusions on other drug. Blood sampling was limited to two timepoints. Infusion-rates of drugs were not collected, and pharmacokinetic modelling was not used. Although the study protocol warranted deep sedation (RASS −4 to −5) data on level of sedation was not collected. Serum concentrations of neuromuscular blocking drugs were not collected. Data on clinical seizures and electroencephalography was not available. The lack of significant differences found could be due to lack of power and needs to be further investigated in large study.

Conclusions

No significant differences in sedative or analgesic drug dosing or concentrations were found between normothermia and hypothermia groups in a multicenter trial with mandatory deep sedation after 40 hours of temperature intervention or at 72 hours after cardiac arrest. These results suggests that hypothermia may not affect the concentration of sedatives and analgesic drugs after cardiac arrest. Overall, time to awakening from sedative discontinuation was also not significantly different between hypothermia and normothermia, indicating no difference in lingering sedative effects. These results need to be confirmed in a larger study.

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CRediT authorship contribution statement

Martin Annborn: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing – review & editing, Supervision, Funding acquisition. **Ameldina Ceric:** Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Visualization, Project administration. **Ola Borgquist:** Investigation, Resources, Formal analysis, Writing – review & editing. **Joachim During:** Investigation, Resources, Formal analysis, Writing – review & editing. **Marion Moseby-Knappe:** Investigation, Resources, Formal analysis, Writing – review & editing. **Anna Lybeck:** Conceptual-

ization, Methodology, Formal analysis, Investigation, Resources, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2023.109831.

Author details

[a]*Anesthesia & Intensive Care, Department of Clinical Sciences Lund, Lund University, Helsingborg Hospital, Helsingborg, Sweden*[b]*Anesthesia & Intensive Care, Department of Clinical Sciences, Lund University, Skane University Hospital, Malmö, Sweden* [c]*Anesthesia & Intensive Care, Department of Clinical Sciences Lund, Lund University, Skane University Hospital, Lund, Sweden* [d]*Neurology, Department of Clinical Sciences Lund, Lund University, Skane University Hospital, Lund, Sweden*

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Effect of level of sedation on outcomes in critically ill adult patients: a systematic review of clinical trials with meta-analysis and trial sequential analysis

Ameldina Ceric,[a,*] Johan Holgersson,[b] Teresa L. May,[c] Markus B. Skrifvars,[d] Johanna Hästbacka,[e] Manoj Saxena,[f,g] Anders Aneman,[h] Anthony Delaney,[i] Michael C. Reade,[j] Candice Delcourt,[k,n] Janus Christian Jakobsen,[l,m] and Niklas Nielsen[b]

[a]Anesthesia & Intensive Care, Department of Clinical Sciences, Lund University, Skane University Hospital, Malmö, Sweden
[b]Lund University, Helsingborg Hospital, Department of Clinical Sciences Lund, Anesthesia & Intensive Care, Lund, Sweden
[c]Maine Medical Center, Department of Critical Care, Portland, Maine, USA
[d]Department of Emergency Care and Services, Helsinki University Hospital and University of Helsinki, Helsinki, Finland
[e]Department of Anesthesiology and Intensive Care, Tampere University Hospital and Tampere University, Tampere, Finland
[f]Division of Critical Care, George Institute for Global Health, Australia
[g]St. George Hospital, South Eastern Sydney Local Health District, Sydney, Australia
[h]Intensive Care Unit, Liverpool Hospital, South Western Sydney Local Health District, South Western Sydney Clinical School, University of New South Wales, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, Australia
[i]The George Institute for Global Health, Sydney, NSW, Australia
[j]Medical School, University of Queensland, Brisbane, QLD, Australia
[k]The George Institute for Global Health, Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia
[l]Copenhagen Trial Unit – Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[m]Department of Regional Health Research, The Faculty of Health Sciences, University of Southern Denmark, Denmark
[n]Department of Clinical Medicine, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, NSW, Australia

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Summary

Background Sedation is routinely administered to critically ill patients to alleviate anxiety, discomfort, and patient-ventilator asynchrony. However, it must be balanced against risks such as delirium and prolonged intensive care stays. This study aimed to investigate the effects of different levels of sedation in critically ill adults.

Methods Systematic review with meta-analysis and trial sequential analysis (TSA) of randomised clinical trials including critically ill adults admitted to the intensive care unit. CENTRAL, MEDLINE, Embase, LILACS, and Web of Science were searched from their inception to 13 June 2023. Risks of bias were assessed using the Cochrane risk of bias tool. Primary outcome was all-cause mortality. Aggregate data were synthesised with meta-analyses and TSA, and the certainty of the evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. This study is registered with PROSPERO: CRD42023386960.

Findings Fifteen trials randomising 4352 patients were included, of which 13 were assessed high risk of bias. Meta-analyses comparing lighter to deeper sedation showed no evidence of a difference in all-cause mortality (risk ratio (RR) 0.94, 95% confidence interval (CI) 0.83–1.06; p = 0.28; 15 trials; moderate certainty evidence), serious adverse events (RR 0.99, CI 0.92–1.06; p = 0.80; 15 trials; moderate certainty evidence), or delirium (RR 1.01, 95% CI 0.94–1.09; p = 0.78; 11 trials; moderate certainty evidence). TSA showed that when assessing mortality, a relative risk reduction of 16% or more between the compared interventions could be rejected.

Interpretation The level of sedation has not been shown to affect the risks of death, delirium, and other serious adverse events in critically ill adult patients. While TSA suggests that additional trials are unlikely to significantly change the conclusion of the meta-analyses, the certainty of evidence was moderate. This suggests a need for future high-quality studies with higher methodological rigor.

*Corresponding author. Anesthesia and Intensive Care, Department of Clinical Sciences Lund, Lund University, Skane University Hospital, Carl Bertil Laurels gata 9, 214 28, Malmo, Sweden.

E-mail addresses: ameldina.ceric@med.lu.se (A. Ceric), johan.holgersson@med.lu.se (J. Holgersson), Teresa.May@mainehealth.org (T.L. May), Markus.Skrifvars@hus.fi (M.B. Skrifvars), johanna.hastbacka@tuni.fi (J. Hästbacka), Manoj.Saxena@health.nsw.gov.au (M. Saxena), Anders.Aneman@health.nsw.gov.au (A. Aneman), anthony.delaney@sydney.edu.au (A. Delaney), m.reade@uq.edu.au (M.C. Reade), cdelcourt@georgeinstitute.org.au (C. Delcourt), jcj_ctu@icloud.com (J.C. Jakobsen), niklas.nielsen@med.lu.se (N. Nielsen).

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Keywords: Systematic review; Meta-analysis; Critically ill; Intensive care; Sedation; Mortality

Research in context

Evidence before this study

In a preliminary search of PubMed, Web of Science, Embase, and Cochrane Library databases, spanning from inception to March 5th, 2024, for each database, we reviewed the existing evidence on the effect of sedation on critically ill adult patients. We used specific search terms "sedation OR hypnotics" AND "critically ill OR critical care OR intensive care" AND "adult" AND "meta-analyses". A systematic review and meta-analyses published in 2020 investigated the effect of light sedation compared to deep sedation in critically ill adults and found that the deeper sedation group had a significantly increased risk for death. In contrast, a meta-analysis published in 2021 showed in meta-analysis of the included randomised trials showed no evidence of a difference in intensive care mortality. Furthermore, a meta-analysis published in 2018 showed lower mortality rate in patients treated with lighter sedation compared with deeper sedation.

Added value of this study

Thus, the previously conducted meta-analyses are inconclusive and this study addresses the limitations of prior meta-analyses by considering the risks of both systematic errors and random errors including Trial Sequential Analysis (TSA), that may enhance the robustness of our analysis and provide a more comprehensive evaluation of the available evidence.

Implications of all the available evidence

This meta-analysis suggests that the level of sedation does not seem to affect the risks of death, serious adverse events, or delirium in critically ill adult patients. While the TSA indicates that additional trials are unlikely to significantly change these findings, the moderate certainty of evidence and the high risk of bias in the included studies highlights the importance for future high-quality trials with increased methodological rigour to ensure more reliable conclusions.

Introduction

Patients with acute serious illnesses who require intensive care admission, also require effective treatment of associated discomfort, anxiety, agitation, and pain that occurs during the process of resuscitation, diagnostics, and subsequent management. The patient's ability to communicate discomfort and pain is often compromised by the several factors including severity of illness, altered mental status, medications, and the need for organ support.[1] Clinical status changes frequently, so clinicians need to continuously assess patient symptoms to assure appropriate titration of sedatives and analgesics.[2,3]

In the short-term, sedatives are primarily used to combat anxiety, agitation, and to prevent patient-ventilator asynchrony. They also decrease the level of consciousness and reduce the capacity of the patient to respond to stimuli and interact with the environment. Sedatives blunt the sympathetic response and may cause cardiovascular dysfunction. In the medium-to long-term, deep sedation is associated with prolonged length of intensive care unit (ICU) stay and associated complications such as delirium.[4,5] Post-traumatic stress disorder is common after acute serious illness and may be related to sedative use or choice of sedative agent.[6–8] By tailoring sedation to the patients' needs and circumstances, health care providers can determine appropriate level of sedation and manage adverse events. This can be achieved by considering patient-related factors such as age, gender, past medical history, the trajectory of the illness, and the pharmacological properties of the agents used.[1,5]

In addition to these considerations, there has been a long-standing discussion about the potential risks and benefits of minimising the depth of sedation, particularly in the general, non-brain-injured ICU population.[1,5,9,10] In patients with brain injury, there is an additional need to manage increased intracranial pressure and seizures and closely monitor the patient's response to stimuli. In practice clinicians often use sedation scales to assess the effect of sedatives on anxiety, agitation, and level of consciousness, to alter the dose of sedatives and target a level of sedation.[5,10] Observational trials have shown a correlation between deeper sedation and adverse outcomes, including mortality and duration of mechanical ventilation.[11,12] However, these studies possess inherent limitations, notably incomplete adjustment for illness severity. For instance, participants who are eligible for lighter sedation are those who are least likely to have poor outcomes. Adjusting for this confounding factor using observed indices of illness severity presents challenges. Randomised clinical trials are the most effective approach to address this confounding. Despite several randomised clinical trials addressing the question, the balance of risk and benefit associated with light sedation is neither

clear nor universally accepted in clinical practice. The previously conducted meta-analyses have some important limitations.[9,13,14] This study addresses the limitations of prior meta-analyses by considering the risks of both systematic errors and random errors including Trial Sequential Analysis (TSA).[15] TSA, a methodology not utilized in previous studies, may enhance the robustness of our analysis, and provide a more comprehensive evaluation of the available evidence. Accordingly, the primary aim of this study was to investigate the association of level of sedation with all-cause mortality by undertaking a quantitative assessment of all relevant published clinical trials. Secondary aims were to identify associations between level of sedation, neurological outcome, and serious adverse events. Our hypothesis was that lighter sedation compared with deeper sedation reduces the risk of death by 25% in critically ill adult patients admitted to the ICU.

Methods

Search strategy and selection criteria

This systematic review, incorporating meta-analyses and trial sequential analysis (TSA) of randomised clinical trials, was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline. The PRISMA checklist was used to guide the reporting process and ensure the inclusion of essential items for a high-quality systematic review. The review protocol was registered prospectively on the international prospective registry of systematic reviews (CRD42023386960), and a pre-specified protocol was published.[16] We searched all relevant databases (Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE, Embase, LILACS, Web of Science Core Collection) from their inception to 13 June 2023 and included randomised clinical trials including critically ill adults admitted to ICU. Trial inclusion required comparison of sedation with no sedation or lighter sedation (however defined by the included study) with deeper sedation. Studies comparing any intervention with one group targeting lighter sedation than the other group, were eligible for inclusion, irrespectively of methods (for example sedations scales, sedation protocol, or type of sedative drug) used to achieve this separation. Studies were not eligible if no separation of targeted sedation depth could be identified.

Data analyses

The primary outcomes were all cause mortality at longest follow-up. Secondary outcomes were serious adverse events at any timepoint, poor neurological outcome (defined by trialists) at longest follow-up, and delirium at any time-point in the ICU admission. Exploratory outcomes were PTSD and duration of mechanical ventilation. In accordance with the Cochrane Handbook for Systematic Reviews of Interventions, two authors independently reviewed each trial for risk of bias, using the second version of the Cochrane risk of bias tool for randomised trials (RoB2).[17] We calculated risk ratios with 95% confidence intervals (CI) by using meta-analyses for dichotomous outcomes. We performed meta-analyses by following the Cochrane Handbook of Systematic Reviews of Interventions, Keus and colleagues, and Jakobsen and colleagues.[18] We used RStudio version 2022.02.3+492 to analyse the data. We combined a visual inspection of forest plots and statistical analyses to identify potential heterogeneity. We performed subgroup analyses (based on type of intervention, follow up time, and risk of bias) for the outcomes all-cause-mortality, serious adverse events and delirium to further investigate heterogeneity and to inspire hypotheses for future studies. Aiming to reduce the risk of type I and II errors, we used a multiplicity adjusted p-value and trial sequential analysis, by dividing the prespecified p value threshold with the value halfway between 1 (no adjustment) and the number of primary and secondary outcome comparisons (Bonferroni adjustment).[15] Cumulative meta-analyses are at risk of random errors due to sparse data and multiple testing of accumulating data. Therefore, TSA can be applied to control these risks (http://www.ctu.dk/tsa/). Similar to a sample size calculation in a randomised clinical trial, TSA estimates the diversity-adjusted required information size (DARIS) (ie, the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) in order to minimise random errors. Using TSA analyses, we pragmatically anticipated an intervention effect equal to a risk ratio reduction (RRR) of 25%, as recommended by the GRADE guidelines when previous evidence do not provide other preliminary estimations.[18] Additionally, we used trial sequential analysis to define the lowest intervention-effects-threshold we can confirm or reject. We used the approach proposed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group for rating the certainty of the evidence.[19] A comprehensive description of the methods is provided in the Supplementary Materials and published protocol.[16]

Ethics approval and consent to participate

No formal approval or review of ethics is required for this systematic review as individual patient data will not be included.

Role of funding source

There was no funding source for this study. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The search strategy defined in the protocol found 17,621 publications that were evaluated to identify trials matching our inclusion criteria. We included a total of

15 trials randomising 4352 participants (Fig. 1).[20–33] Funnel plot of included trials showed a symmetrical distribution around the effect estimate (risk ratio) suggesting minimal risk of publication bias (see Supplement Figure S1). Linear regression of the funnel plot (Egger's statistics) was not significant (intercept –0.1953, standard error = 0.56, p-value = 0.73) and this supported the visual inspection of the funnel plot that there are no clear signs of publication bias. Four trials with 2084 participants compared no sedation with sedation. Eleven trials involving 2268 participants were included to compare different sedation levels. Among these trials, four focused on comparing daily interruption of sedatives to continuous sedation, one trial compared intermittent sedation to daily interruption of sedatives, and two trials compared lighter sedation (defined as Motor activity assessment scale (MAAS) 3–4 or Modified Ramsey sedation scale level 1–2) to deeper sedation (defined as MAAS 1–2 or Modified Ramsey sedation scale level 3–4). Additionally, only four trials specified the type of sedative used, comparing dexmedetomidine to other sedatives. The characteristics of included studies and definition of the separation of sedation levels are presented in Supplement Table S1. Most participants (1843 in 12 trials) were hemodynamically unstable, and 1550 participants (10 trials) had respiratory failure. A minority of participants (150 participants in 7 trials) were trauma participants, 7 participants (1 trial) were neurologically injured participants, and no trials reported cardiac arrest participants. We assessed 13 trials as being of high risk of bias and 2 trials of being low risk of bias (Fig. 2). The most common reason for high risk of bias was the lack of successful blinding to treating clinicians which introduces potential bias through deviations from the intended intervention. The 15 included trials (Fig. 1) were included in meta-analyses. Missing data on the primary outcome constituted <5% of the overall data, and we

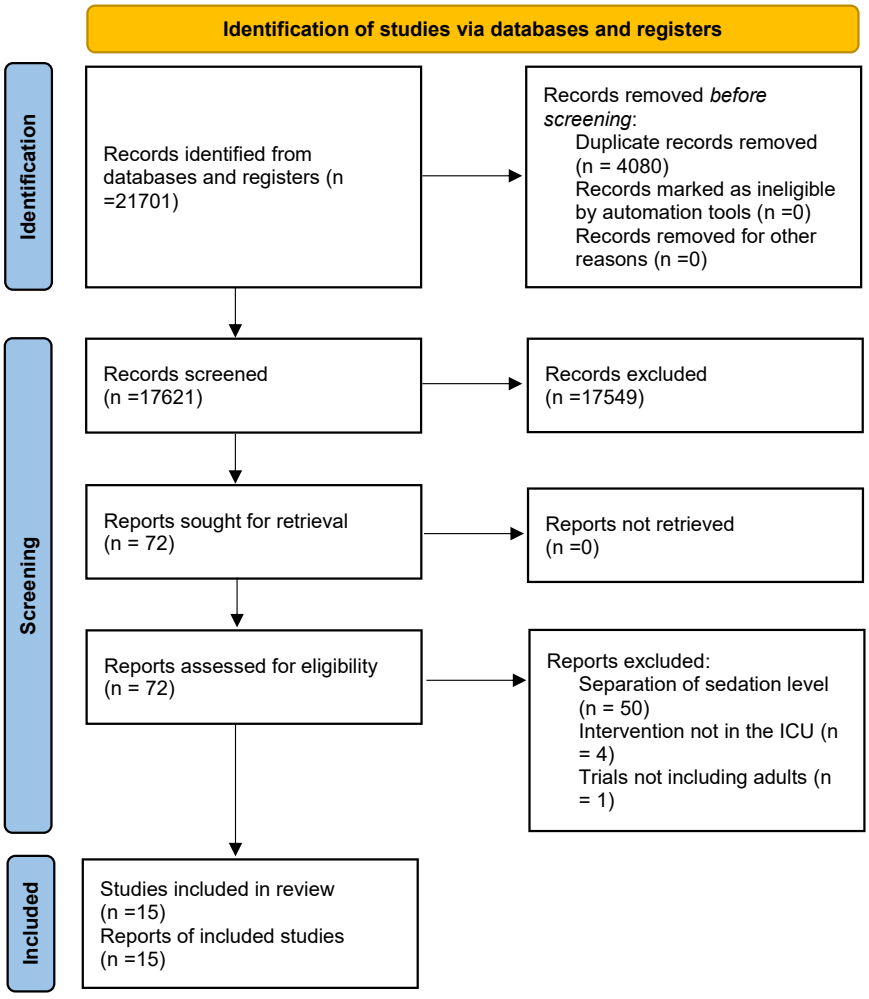

Fig. 1: **PRISMA flow diagram outlining study inclusion.**

***Fig. 2:* Risk of bias summary**. Risk of bias summary for randomised controlled trials included in evidence. Synthesis. Risk of bias assessment used Cochrane risk of bias tool 2 (RoB2). D1, bias arising from randomisation process; D2, bias due to deviations from intended intervention; D3, bias due to missing outcome data; D4, bias in measurement of outcome; D5, bias in selection of reported result. +, low risk; ?, some concerns; -, high risk? [a] This is regarding all-cause mortality and serious adverse event as outcome. [b] High risk for outcomes delirium and duration of mechanical ventilation. [c] High risk for the outcome PTSD. [d] High risk of bias for the duration of mechanical ventilation outcome. [e] High risk for outcome delirium.

deemed the impact of missing data to be low; therefore, we did not perform sensitivity analyses.

Primary outcome

All-cause mortality

Fifteen trials with a total of 4352 participants reported all-cause mortality. A total of 739 (33.9%) of 2177 in the lighter sedation group died compared to 748 (34.3%) of 2175 in the deeper sedation group. The timing of outcome assessment varied between trials, ranging from 28 days to 356 days after randomisation. Meta-analysis showed no evidence of a difference in all-cause mortality (risk ratio 0.94, 95% CI 0.83–1.06; I^2 = 20%; p = 0.28; 15 trials; moderate certainty evidence) (Fig. 3; Table 1). Visual inspection of the forest plot and quantitative measures of heterogeneity (I^2 = 20.0%) did not show clear signs of heterogeneity (Fig. 3). TSA showed that a relative risk reduction of 16% or more between the compared interventions could be rejected (Figs. 4 and 5). We assessed this outcome result as high risk of bias and the certainty of the evidence as moderate (Table 1).

Secondary outcomes

Serious adverse events

Fifteen with a total of 4352 participants reported on serious adverse events. The most commonly reported serious adverse events (SAEs) included death (68.1% of all reported SAE) and secondary delirium (31.9% of all reported SAE). The assessment time points varied between trials, ranging from 28 days to hospital discharge, to 365 days after randomisation. A total of 883 (40.6%) of 2177 trial participants had a serious adverse event in the lighter sedation group compared with 893 (41.1%) of 2175 in the deeper sedation group. Meta-analysis showed no evidence of a difference (risk ratio 0.99, 0.92–1.06; I^2 = 0%; p = 0.80; 15 trials; moderate certainty evidence) (Supplement Figure S2; Table 1). Quantitative assessment of heterogeneity (I^2 = 0%) combined with visual inspection of the forest plot did not show signs of significant heterogeneity (Supplement Figure S2). TSA showed that a relative risk reduction of 9% or more between the compared interventions could be rejected (Supplement Figure S3 and S3a).

Neurological outcome

No trials reported on neurological outcome.

Delirium

Eleven trials with a total of 3368 participants reported on delirium. Eight trials used Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), one used Diagnostic and Statistical Manual fourth edition (DSM-IV), and one used intensive care screening delirium checklist.[34–36] The assessment time points varied between trials, ranging from 48 h, to ICU, to hospital discharge, to 28 days after randomisation. A total of 570 (33.9%) of 1681 trial participants had delirium in the lighter sedation group compared with 561 (33.2%) of 1687 in the deeper sedation group. Meta-analysis showed no evidence of a difference (risk ratio 1.01, 95% CI 0.94–1.09; p = 0.78; 11 trials; moderate certainty

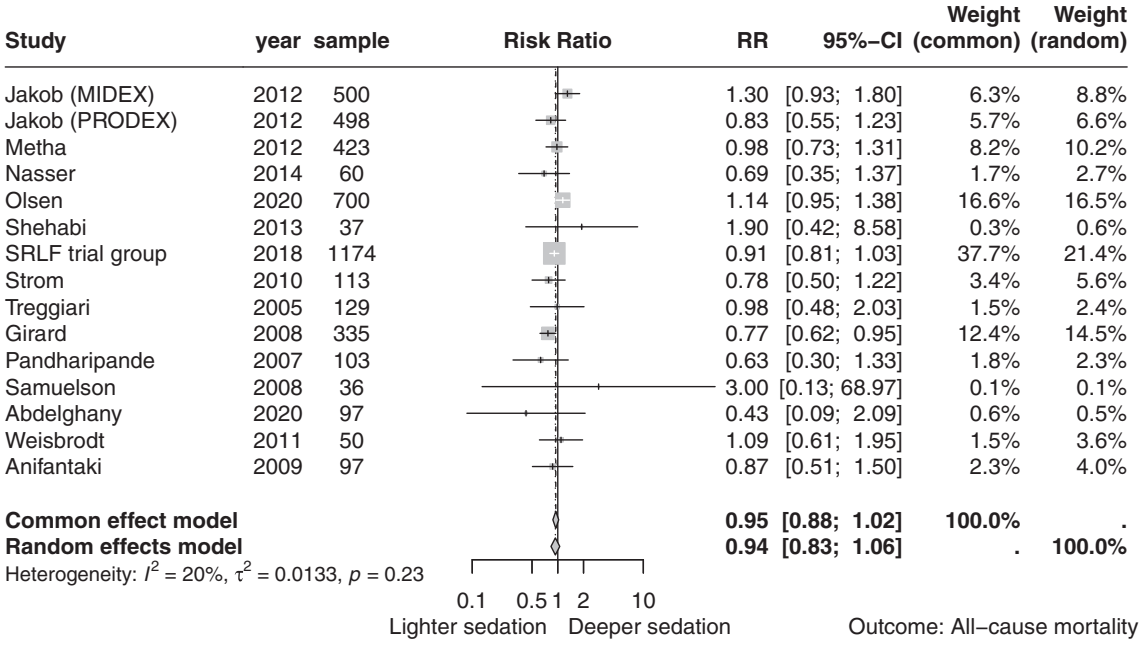

***Fig. 3:* Random effects meta-analysis comparing lighter sedation versus deeper sedation for all-cause mortality.** Random effects meta-analysis comparing lighter sedation versus deeper sedation for all-cause mortality (risk ratio 0.94, 95% confidence interval 0.83–1.06; p-val = 0.23; I^2 = 20%; 15 trials). The risk ratios show a favor of lighter sedation to the left and deeper sedation to the right.

evidence) (Supplement Figure S4; Table 1). Quantitative measures of heterogeneity (I^2 = 20%) combined with visual inspection of the forest plot did not show signs of significant heterogeneity (Supplement Figure S4). TSA showed that a relative risk reduction of 12% or more between the compared interventions could be rejected (Supplement Figure S5 and 5a).

Exploratory outcomes

Duration of mechanical ventilation

Five trials including 1024 participants reported on the duration of mechanical ventilation. Meta-analyses showed no evidence of a difference (mean difference –0.91 (CI –2.01 to 0.18), p = 0.10; I^2 = 0%; 5 trials) (Supplement Figure S6). Quantitative measures of heterogeneity (I^2 = 0%) combined with visual inspection of the forest plot did not show signs of significant heterogeneity (Supplement Figure S6).

Posttraumatic stress disorder

One study (60 participants) reported higher median scores in the lighter sedation group using Impact of Event Scale, indicating higher psychological distress at 6 months follow up.[37] Two studies (138 participants) used Impact of Event Scale Revised to report on posttraumatic stress disorder (PTSD) 2 months and 4 weeks follow up.[38] Six (8.6%) out of 70 participants had PTSD in the lighter sedation group and 6 (8.8%) out of 68 participants had PTSD in the deeper sedation group. Meta-analysis showed no evidence of a difference (risk ratio 0.97, 95% CI 0.33–2.85; p = 0.95) (Supplement Figure S7). Quantitative measures of heterogeneity (I^2 = 0%) combined with visual inspection of the forest plot did not show signs of significant heterogeneity (Supplement Figure S7).

Other exploratory outcomes

No studies reported data on quality of life, mean arterial blood pressure, body core temperature, or intracranial pressure.

Subgroup analyses

None of the prespecified subgroup analyses showed evidence of a difference (Supplement Figures S8–S16).

Discussion

In this systematic review with meta-analyses and trial sequential analysis of data from 15 randomised clinical trials and 4352 participants with moderate-level evidence, we showed that level of sedation did not seem to affect the risk of death in critically ill adults, based on studies conducted to 13 June 2023. We found almost no signs of statistical heterogeneity, and none of the predefined subgroup analyses showed evidence of a difference in all-cause mortality, which supports the validity of our meta-analysis results. We found no evidence that the level of sedation affected delirium or other serious adverse events. Further, we found no evidence that the level of sedation affected duration of

Lighter sedation compared to deeper sedation in critically ill adult patients.

Patients or population: Critically ill adult patient admitted to intensive care unit.
Setting: Admitted to intensive care unit.
Intervention: Lighter sedation.
Control: Deeper sedation.

Outcome	Anticipated absolute effect size (95% CI)[c]		Relative effect size (95% CI)	No of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with control	Risk with intervention				
All-cause mortality (follow up range: 28 days–365 days)	343 per 1000	339 per 1000	RR: 0.94 (0.83, 1.06)	4352 (15 RCT)	Moderate[a]	Risk of bias: Serious Inconsistency: No Indirectness: No Imprecision: No Publication bias: No
Serious adverse events (follow up range: 28 days–365 days)	411 per 1000	406 per 1000	RR: 0.99 (0.92, 1.06)	4352 (15 RCT)	Moderate[a]	Risk of bias: Serious Inconsistency: No Indirectness: No Imprecision: No Publication bias: No
Delirium (follow up range: 7 days–45 days)	332 per 1000	339 per 1000	RR: 1.01 (0.94, 1.09)	3368 (11 RCT)	Moderate[a]	Risk of bias: Serious Inconsistency: No Indirectness: No Imprecision: No Publication bias: No
PTSD (follow up range: 4 weeks-2 months)	88 per 1000	85 per 1000	RR: 0.97 (0.33, 2,85)	138 (2 RCT)	Low[a,b]	Risk of bias: Serious Inconsistency: No Indirectness: No Imprecision: yes Publication bias: No

RR: Risk ratio CI: Confidence interval; GRADE: GRADE Working Group grades of evidence. GRADE Working Group grades of evidence. High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. Explanations: [a]Downgraded one for risk of bias. [b]Downgraded one for imprecision due to small sample size and wide confidence intervals. [c]The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Table 1: **Summary of findings table for lighter sedation versus deeper sedation.**

mechanical ventilation or post-traumatic stress disorder. Finally, we found insufficient evidence to confirm or reject the hypothesis that the level of sedation affected neurological outcome. Among the fifteen included studies, thirteen were deemed to have a high risk of bias, primarily due to deviations from the intended intervention. The lack of blinding in the study designs extended to treating clinicians and outcome assessors, who were aware of trial participants' targeted sedation levels. This could have influenced medical decisions, potentially leading to adjustments in sedative dosages and other treatment approaches. Consequently, unintended deviations from the planned intervention might have affected patient outcomes, impacting factors such as recovery trajectories and clinical assessments. This could impact the validity and reliability of the study results, thus the overall level of evidence of these studies is moderate. The high risk of bias in these studies suggests a need for future studies with higher methodological rigor to address this limitation and provide more reliable results. It is difficult to blind the immediate treatment providers and patients to the allocated sedation level, however, other health care providers, outcome assessors, statisticians, and authors may be blinded to reduce the impact of not being able to blind the immediate treatment providers and patients.

The effects of different levels of sedation in critically ill patients remain uncertain, and consequently, the optimal assessment time point of mortality for such patients are not established. It is crucial to ensure that the duration of observation is sufficiently extended to allow physiological processes the necessary time to result in observable clinical events. However, the observation period must not extend too long, this might introduce events unrelated events to the intervention to occur, which might compromise the statistical power. Hence, for our primary analyses, we pragmatically selected the time to longest follow up a prior, adhering to this decision irrespectively of the study design or results, in accordance with the protocol.[16]

Our study included randomised clinical trials where it was possible to separate between different levels of sedation, regardless of the methodological approach used to define the targeted sedation level. The SPICE-III trial, comparing dexmedetomidine with usual sedation, aimed for "light sedation" using the RASS scale in both

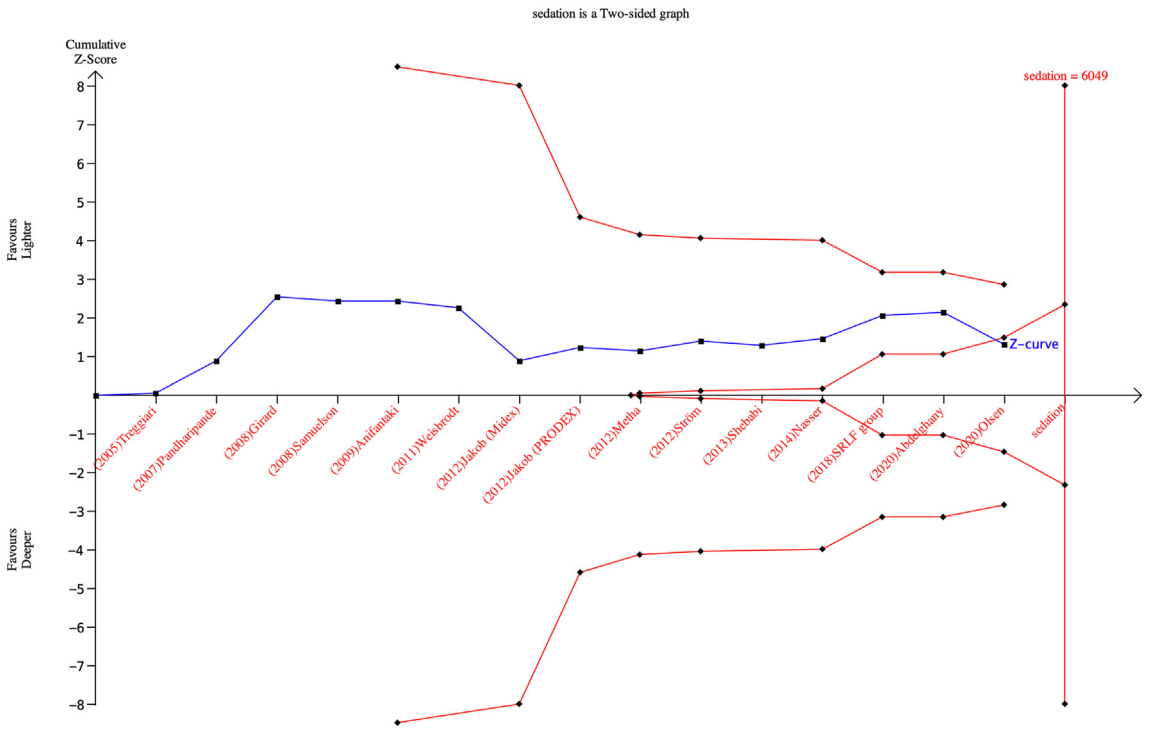

Fig. 4: **Trial sequential analysis (TSA) of lighter sedation versus deeper sedation for all-cause mortality**. Two-sided TSA graph of lighter sedation versus deeper sedation for all-cause mortality in 15 trials. Diversity-adjusted required information size (DARIS) was calculated on basis of all-cause mortality proportion in control group of 36.4%, relative risk reduction of 16% in experimental group, type I error (α) of 2%, and type II error (β) of 10% (90% power). Required information size was calculated to be 7085 participants. Cumulative z curve (red lines above and under) did not cross trial sequential monitoring boundaries for either benefit or harm. Cumulative z curve did cross inner wedge futility line (red outward sloping lines).

groups.[39] As a result, there was no separation of targeted sedation levels, making it ineligible for inclusion in this review. Notably, despite a slightly higher proportion of patients with lighter RASS scores in the dexmedetomidine group (56.6% vs. 51.8%), no significant difference in outcomes was observed among the 4000 randomized patients. We included studies that used a protocolised approach to sedation, where one protocol aimed to achieve a lighter sedation level than the other group. The method used to achieve the targeted sedation level was not a criterion for study inclusion. Two studies used sedation scales (MAAS and modified Ramsey sedation scale) to differentiate between levels of sedation, but they used different types of sedation scales, and the approach was not consistent. It should be noted that using sedation scales to define levels of sedation is not inherently better or worse than other methods, and similarly, the protocolised sedation approach employed in three other studies (using daily interruption of sedatives or intermittent sedation as the lighter sedation group and continues as the deeper sedation group) is not necessarily superior. However, the difference in how the sedation scales were used in the two studies and the variation in the protocolised sedation approach used in these studies prevent direct comparisons of these results. Additionally, it should be noted that in some studies, the lighter sedation group may correspond to the deeper sedation group in other studies, making direct comparisons across studies classifying the groups into deeper versus lighter sedation even more challenging. For instance, two study used no sedation versus sedation with daily interruption, while three studies compared daily interruption with continuous sedation. The variation in sedation approaches, study design, and methods used to define sedation levels can make it challenging to interpret the results of these meta-analyses. The fact that different studies used different sedation protocols, sedation scales, or no sedation at all, means that the sedation levels achieved in the studies may not be directly comparable. Although our study did not find significant evidence of heterogeneity, it is essential to note that our results primarily demonstrate the effect of lighter sedation compared to deeper sedation aiming to achieve similar outcomes, regardless of the specific method used to achieve the targeted sedation level.

While the included studies used various methodologies to achieve the targeted sedation level, including

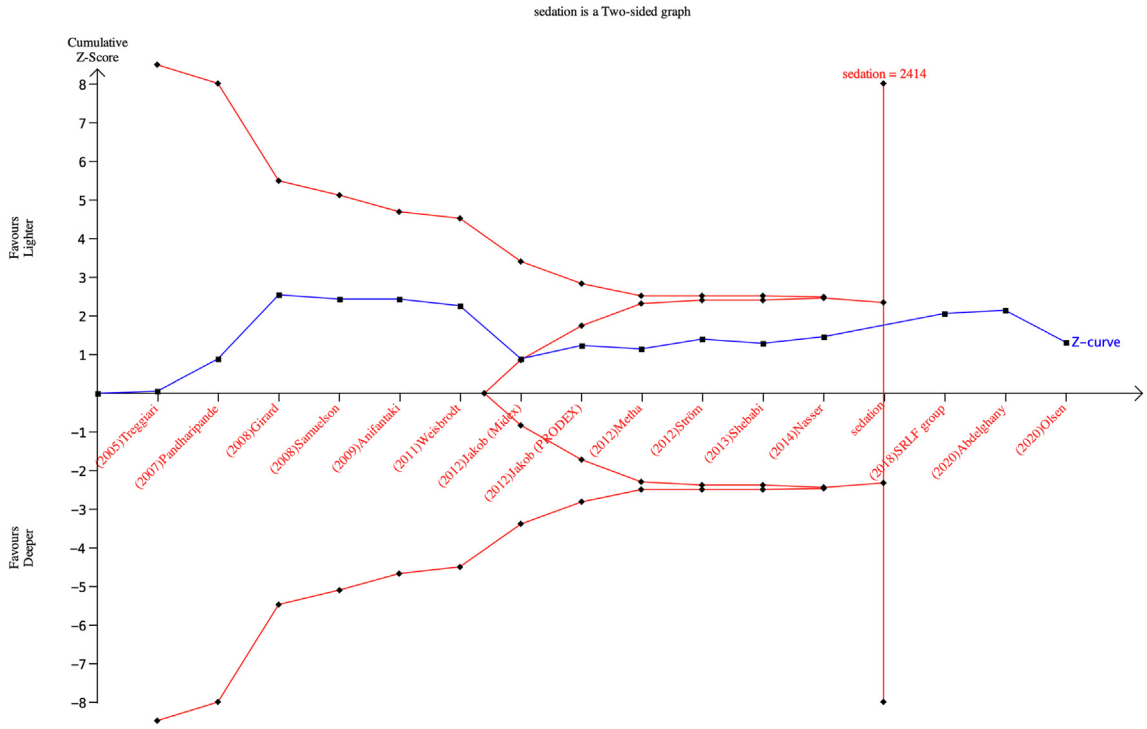

Fig. 5: **Trial sequential analysis (TSA) of lighter sedation versus deeper sedation for all-cause mortality**. Two-sided TSA graph of lighter sedation versus deeper sedation for all-cause mortality in 15 trials. Diversity-adjusted required information size (DARIS) was calculated on basis of all-cause mortality proportion in control group of 36.4%, relative risk reduction of 25% in experimental group, type I error (α) of 2%, and type II error (β) of 10% (90% power). Required information size was calculated to be 2824 participants. Cumulative z curve (red lines above and under) did not cross trial sequential monitoring boundaries for either benefit or harm. Cumulative z curve did cross inner wedge futility line (red outward sloping lines).

sedation scales, protocolised sedation, interruption of sedatives, and no sedation; the results showed consistent effects of lighter sedation compared to deeper sedation. Although this variation in methodology may limit the reliability of the results, the fact that subgroups of these different methodologies also showed the same results increases the confidence in the overall findings. Nevertheless, the results should be interpreted cautiously, and further investigation and consideration of the various methodologies addressed in future studies. The lack of consensus on the definition of light, moderate, and deep sedation makes it challenging to evaluate the effect of the level of sedation on critically ill patients. Confounding factors, such as the severity of illness and underlying condition also affect the assessment of sedation depth. Therefore, investigating the effect of sedation is complex and warrants further high-quality studies to optimise care in critically ill adult patients.

TSA crossed the line of futility which adds to the robustness of our findings. Even though this suggests that additional trials are unlikely to change the conclusion of the meta-analyses significantly, it is essential to consider the moderate quality evidence included in the TSA, as this can impact the reliability and strength of the conclusion. Dealing with low-moderate quality evidence and high risk of bias can result in over- or underestimation of the true effect size. Therefore, when interpreting the TSA which are based on the effect estimate, it is important to consider the potential for bias and imprecision in the included trials. Thus, further research with similar methodologies used are unlikely to result in new findings, this study shows that future research must include refined methods and patient selection to determine if the level of sedation effects mortality. Specifically, future studies should aim to address the limitations of current evidence by using standardised methodology to assess the sedation depth and blinding of study participants and outcome assessors to reduce the risk of bias.

Our review has several strengths. Our method was predefined in detail, and the protocol was published before we performed our literature search. We searched all relevant databases, used an eight-step assessment suggested by Jakobsen and colleagues to assess our results' clinical significance, and we used TSA to reduce the risks of type I and type II errors.[15] Furthermore, we did meta-analyses with both fixed effects and random

effects meta-analysis, we investigated subgroup differences, and we assessed the certainty of the evidence through GRADE.

The main limitation of our review is the low-moderate methodological quality of the included trials, with most of the included trials were at high risk of bias. The inclusion of active comparator trials is a potentially complicating factor regarding interpretation of the results. The limitation of including active comparator trials (lighter versus deeper sedation, dexmedetomidine versus propofol, midazolam, and lorazepam, daily interruption versus continuous sedation) compared to intervention versus control (no sedation versus sedation) can complicate the interpretation of the results, as the results of active comparator trials can be influenced not only by the level of sedation but also by choice of sedatives and factors such as patient characteristics or clinical setting. Similarly, in trial comparing dexmedetomidine versus propofol, differences in pharmacological properties of the two drugs may impact the results, in addition to differences in the level of sedation. However, in the absence of heterogeneity between trials, as in our study, this should not be considered limiting to our results. Aiming to be inclusive, we accepted various patients and interventions. Furthermore, it is important to consider that the randomised clinical trials may have a potential weakness in this context, as they may not have included the sickest adult critically ill patients due lack of equipoise regarding lighter or deeper sedation. As a result, the trials may not have provided a comprehensive representation of the entire critically ill population. The inclusion of the most severely ill patients in the trials might have limited the ability to detect a mortality benefit associated with either lighter or deeper sedation strategies, leaving the question unanswered. Another limitation is in the secondary outcome delirium, where the assessment quality varies among studies, potentially impacting results. For instance, assessment frequency differs, ranging from one timepoint to daily assessments, and some studies lack detailed descriptions of the assessment methodology.

Guidelines suggest targeting lighter sedation or using daily awakening test to improve short-term outcomes, with low quality evidence.[1,40] This study shows that lighter sedation compared to deeper sedation does not seem to affect mortality and other selected outcomes. However, it remains unknown whether this applies regardless the methods used to achieve the targeted sedation such as choice of sedative drug, choice of sedation scale used, or protocolised sedation. Our results suggest little to no difference in effect of the level of sedation, and we could reject a relative risk reduction of at least 16%. We acknowledge that a relative risk reduction of less than 16% may still be clinically relevant. Level of sedation may be investigated in further adequately powered high quality randomised trials, including a health economics perspective, to define implications for patients and society. Moreover, there is a notable paucity of studies specifically investigating the optimal level of sedation in patient populations such as brain injured patients and cardiac arrest patients, who pose unique challenges in sedation management. These critical patient groups, which often require intensive care management, are frequently excluded from randomised clinical trials assessing sedation strategies in critically ill patients. In particular, altered consciousness and neurological deficits in brain injured patients contribute to the complexity of accurately assessing and monitoring sedation levels, making using sedation scales difficult. Consequently, the generalisability of our findings to these relevant populations remains to be determined.

In summary, the level of sedation did not seem to affect the risks of death, serious adverse events, or delirium in critically ill adult patients. While the TSA suggests that additional trials are unlikely to significantly change the conclusion of the meta-analyses, the certainty of the evidence was only moderate. This suggests a need for future high-quality trials with increased methodological rigour to address this limitation and provide more reliable results.

Contributors

AC, JCJ, and NN have substantially contributed with the concept and design of the work. AC has drafted the work and analysed the data. AC and JH accessed and verified the underlying data. All authors (AC, JHo, TLM, MBS, JHä, MS, AA, AD, MCR, CD, JCJ, and NN) had full access to the data, and have substantially contributed with interpreting the data and revised the work. All authors had final responsibility for the decision to submit for publication.

Data sharing statement

All data generated or analysed during this study are included in this published article and its supplementary information files. Extracted data are available on request to the corresponding author.

Declaration of interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: TLM declares that her institution received grants (ICECAP (UG3HL134269)) for her role as site principal investigator for SIREN funded RCT for cardiac arrest patients and are on clinical standardization committee. TLM's institution has secured funding for her involvement as a co-investigator in an ancillary study related to ICECAP, with a 5% Full-Time Equivalent support allocation (PRECICECAP (R01NS119825)). Additionally, TLM is principial investigator for a grant, reducing rural disparities in cardiac arrest outcomes by standardization of care (P20GM139745)), with 50% FTE support with funds to the institution. MSk received speakers fee 2021 and 2022 for BARD Medical (Ireland). JHä declares that she received grants from Paulo Foundation, Tor och Kirsti Johanssons Hjärt och Cancerstiftelse, Finska Läkaresällskapet, NordForsk, and Government funding for University Level research (2021, 2022, and 2023). JHä also declared that her institution (Tampere University Hospital research services) received a consultation fee from Paion and that JHä participated on Data Safety Monitoring Board or Adversary Board in Paion. JHä also received payment for lectures for Finnish Medical association, Laboratory Medicine, and Duodecim (a Finnish society of physicians). Additionally, JHä has a role in Educational Committee of Scandinavian Society of Anaesthesiology, board member of Advanced Educational Committee of Intensive Care Medicine in Scandinavian Society of Anaesthesiology and Intensive Care Medicine, and European Society of

Intensive Care Medicine: National representative and faculty in CoBaTriCe Finnish Sepsis Society and have minor share of Orion B stock. MCR declare that his institution (University of Queensland) received grant support from National Health and Medical Research Council, Australia, Medical Research Future Fund, and Intensive Care Foundation, Australian Defence Force, and Royal Brisbane and Women's Hospital Foundation the past 36 months. MCR also received payment for expert testimony (in cases not related to the subject matter of this paper) from government of the Northern Territory High Court of New Zealand, received payment for being a member of DSMB for clod stored platelet trial, and his wife had stock investment in ETF that includes biomedical shares, which were sold 12 months ago. NN declared that his institution received support for the present study from Swedish Research Council and governmental funds within the Swedish Health Care (ALF). All other authors declared no conflicts of interests.

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Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102569.

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RESEARCH ARTICLE

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Continuous deep sedation versus minimal sedation after cardiac arrest and resuscitation (SED-CARE): A protocol for a randomized clinical trial

A. Ceric[1] | J. Dankiewicz[2] | J. Hästbacka[3] | P. Young[4,5,6,7] | V. H. Niemelä[8] | F. Bass[9,10] | M. B. Skrifvars[8] | N. Hammond[11,12] | M. Saxena[13] | H. Levin[14,15] | G. Lilja[16,17] | M. Moseby-Knappe[14,18] | M. Tiainen[19] | M. Reinikainen[20,21] | J. Holgersson[22,23] | C. B. Kamp[24,25] | M. P. Wise[26] | P. J. McGuigan[27,28] | J. White[26] | K. Sweet[29] | T. R. Keeble[30,31] | G. Glover[32] | P. Hopkins[33,34] | C. Remmington[35,36] | J. M. Cole[37] | N. Gorgoraptis[38] | D. G. Pogson[39] | P. Jackson[40] | J. Düring[41] | A. Lybeck[42] | J. Johnsson[43] | J. Unden[44,45] | A. Lundin[46] | J. Kåhlin[47,48] | J. Grip[49,50] | E. M. Lotman[51] | L. Romundstad[52,53] | P. Seidel[54] | P. Stammet[55,56] | T. Graf[57,58] | A. Mengel[59] | C. Leithner[60] | J. Nee[61] | P. Druwé[62] | K. Ameloot[63] | A. Nichol[64,65,66] | M. Haenggi[67] | M. P. Hilty[68] | M. Iten[69] | C. Schrag[70] | M. Nafi[71] | M. Joannidis[72] | C. Robba[73] | T. Pellis[74] | J. Belohlavek[75,76] | D. Rob[77] | Y. M. Arabi[78] | S. Buabbas[79] | C. Yew Woon[80,81,82] | A. Aneman[83,84,85] | A. Stewart[86] | M. Reade[87] | C. Delcourt[88,89] | A. Delaney[90] | M. Ramanan[91,92,93] | B. Venkatesh[9] | L. Navarra[5] | B. Crichton[5] | A. Williams[94] | D. Knight[95] | J. Tirkkonen[96] | T. Oksanen[97] | T. Kaakinen[98,99] | S. Bendel[20,21] | H. Friberg[100,101] | T. Cronberg[16,17] | J. C. Jakobsen[102,103] | N. Nielsen[22,23]

Correspondence
A. Ceric, Department of Clinical Sciences Lund, Anesthesia and Intensive Care, Skane University Hospital, Carl Bertil Laurels gata 9, 214 28 Malmo, Sweden.
Email: ameldina.ceric@med.lu.se

Funding information
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Abstract

Background: Sedation is often provided to resuscitated out-of-hospital cardiac arrest (OHCA) patients to tolerate post-cardiac arrest care, including temperature management. However, the evidence of benefit or harm from routinely administered deep sedation after cardiac arrest is limited. The aim of this trial is to investigate the effects of continuous deep sedation compared to minimal sedation on patient-important outcomes in resuscitated OHCA patients in a large clinical trial.

For affiliations refer to page 9

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Methods: The SED-CARE trial is part of the 2 × 2 × 2 factorial *Sedation, Temperature and Pressure after Cardiac Arrest and Resuscitation* (STEPCARE) trial, a randomized international, multicentre, parallel-group, investigator-initiated, superiority trial with three simultaneous intervention arms. In the SED-CARE trial, adults with sustained return of spontaneous circulation (ROSC) who are comatose following resuscitation from OHCA will be randomized within 4 hours to continuous deep sedation (Richmond agitation and sedation scale (RASS) −4/−5) (*intervention*) or minimal sedation (RASS 0 to −2) (*comparator*), for 36 h after ROSC. The primary outcome will be all-cause mortality at 6 months after randomization. The two other components of the STEPCARE trial evaluate sedation and temperature control strategies. Apart from the STEPCARE trial interventions, all other aspects of general intensive care will be according to the local practices of the participating site. Neurological prognostication will be performed according to European Resuscitation Council and European Society of Intensive Care Medicine guidelines by a physician blinded to the allocation group. To detect an absolute risk reduction of 5.6% with an alpha of 0.05, 90% power, 3500 participants will be enrolled. The secondary outcomes will be the proportion of participants with poor functional outcomes 6 months after randomization, serious adverse events in the intensive care unit, and patient-reported overall health status 6 months after randomization.

Conclusion: The SED-CARE trial will investigate if continuous deep sedation (RASS −4/−5) for 36 h confers a mortality benefit compared to minimal sedation (RASS 0 to −2) after cardiac arrest.

KEYWORDS
cardiac arrest, randomized clinical trial, sedation

1 | BACKGROUND AND SIGNIFICANCE

Approximately 700,000 individuals suffer from out-of-hospital cardiac arrest (OHCA) annually in Europe and in the United States.[1–3] After resuscitation from cardiac arrest and regaining spontaneous circulation, most cardiac arrest patients remain unconscious and require intensive care treatment.[4,5] The post-cardiac arrest period involves many clinical decisions, including ventilator strategy, hemodynamic targets, vasopressor support, organ support, withdrawal of life-sustaining therapies, and providing patient comfort through sedation and analgesia.[6–8] Temperature management is the only intervention that has been recommended by guidelines to reduce hypoxic–ischemic brain injury and increase the likelihood of a good functional outcome; however, it has limited supportive evidence.[6]

For general intensive care unit (ICU) patients, current guidelines recommend minimizing sedation through daily interruptions of sedative infusions or using a protocol targeting light sedation.[9–11] In post-cardiac arrest care, short-acting sedatives and opioids are recommended during targeted temperature management (TTM) to ensure patient comfort and reduce shivering, but with sedation breaks advised only after rewarming.[12,13] Additionally, approximately one third of cardiac arrest patients have seizures, which could further aggravate the hypoxic brain injury.[14] Sedation, a powerful anti-seizure strategy, has been proposed as a potentially brain-protective and seizure-prophylactic intervention based on physiological reasoning and some experimental studies.[15–17] Sedation may also support brain protection by enhancing glymphatic system function through inducing non-rapid eye movement (REM) sleep, which helps clear toxic breakdown products such as β-amyloid and tau-protein, potentially reducing the risk of neurodegeneration.[18,19]

While sedation can provide benefits by alleviating discomfort, pain, and anxiety as well as facilitating necessary procedures and treatments, it is important to consider the associated risks. Deeper sedation can compromise circulatory and respiratory functions and increase the risk of adverse effects like pneumonia, delirium, delayed awakening and mobilization, and prolonged ICU stay, which may negatively affect outcome.[20–24] In addition, sedation interferes with neurological prognostication as it confounds clinical neurologic examination of consciousness and may alter electroencephalography (EEG) patterns.[25–27]

Sedation depth is most effectively monitored using clinical sedation assessments such as the Richmond Agitation and Sedation Scale (RASS) a well-established, validated, and reliable sedation scale for general ICU patients.[28,29] However, comatose cardiac arrest patients have been excluded in the development of sedation scales to avoid confounding interaction between unresponsiveness due to brain

injury and sedation, making the assessment of sedation depth in these patients difficult.[28,29]

In cardiac arrest patients with hypoxic–ischemic encephalopathy, it is unclear whether the potential benefits of sedation outweigh the detrimental effects. In the context of these conflicting arguments for and against deep sedation in the first days following cardiac arrest, there is substantial uncertainty as to optimal clinical practice.

Here, we describe the Sedation after Cardiac Arrest and Resuscitation (SED-CARE) trial, which is part of the factorial STEPCARE randomized clinical trial. The two other interventions of the STEPCARE trial (temperature and blood pressure) are described separately.

2 | METHODS

2.1 | Trial design

The SED-CARE trial is registered at clinicaltrials.gov (NCT05564754, 2022-10-03) as part of the 2 × 2 × 2 factorial STEPCARE trial. The STEPCARE trial protocol was designed following the SPIRIT guidelines, and the trial will be reported according to the CONSORT guidelines.[30–32] The full STEPCARE trial protocol is available at https://stepcare.org/. The STEPCARE trial is a randomized international, multicenter, parallel-group, investigator-initiated, superiority trial with three simultaneous intervention arms, considered three separate trials. In the SED-CARE trial, participants will be randomized to cardiac arrest management with continuous deep sedation for 36 h or minimal sedation. In the two other interventions, participants will be randomized to fever treatment with or without a device and to higher or lower mean arterial blood pressure treatments. Apart from the interventions of the STEPCARE trial, intensive care management will be according to international guidelines and the local practices of each participating hospital.

2.2 | Inclusion criteria

SED-CARE will include adults (≥18 years) who experience an OHCA with sustained return of spontaneous circulation (ROSC; 20 min of spontaneous circulation without the need for chest compressions) and who are unconscious, defined as not being able to obey verbal commands (Full Outline of UnResponsiveness [FOUR] score motor response <4) or who are intubated and sedated because of agitation after sustained ROSC.[33] Participants must not have treatment limitations for intensive care (e.g., a "do not attempt resuscitation" order or a decision not to escalate care) to be included in the trial. Screening will be performed as soon as possible but no later than 4 h after ROSC.

2.3 | Exclusion criteria

Exclusion criteria will be trauma or hemorrhage (including gastrointestinal bleeding) as the presumed cause of the arrest, pregnancy, suspected or confirmed intracranial hemorrhage, and previous randomization to the STEPCARE trial. Additionally, patients treated with extracorporeal membrane oxygenation (ECMO) prior to randomization will be excluded.

2.4 | Screening and randomization

Screening will be performed in the emergency room, angiography suite, or the ICU. Clinical investigators at each participating site will be responsible for the screening of all patients who are resuscitated from an OHCA. A screening log will be compiled, including all patients with sustained ROSC admitted to the ICU, to document whether they are eligible for inclusion. Informed consent will be obtained according to national ethical approvals. The reason for the exclusion of screened patients will be documented and reported. Randomization will be performed via a web-based application to allow for immediate allocation to treatment groups and to ensure allocation concealment and adequate allocation sequence generation. Randomization will be performed with blinded permuted blocks of varying sizes, stratified for trial site.

2.5 | Intervention

The intervention will begin immediately after randomization by adjusting sedative infusions and administrations to the targeted sedation level. However, if needed, patients can be initially sedated to ensure safe transport, imaging, coronary angiography, and other invasive procedures. The sedation depth will be assessed and determined using the RASS. The RASS score ranges from −5 (un-arousable) to 0 (alert and calm) to +4 (combative). RASS −4 to −5 is unresponsive to voice and considered deep sedation, while a RASS score of 0 to −3 is a patient responsive to voice and considered light sedation. The RASS score and motor response (defined as obeying commands) will be recorded every 4 h.

In both study groups, multimodal pain management will be adopted, including non-pharmacological techniques, acetaminophen (paracetamol), and opioids by either continuous or intermittent intravenous infusion. Pain management and treatment for delirium should follow the principles outlined by the Society of Critical Care Medicine (SCCM).[34] Thus, in both study groups, sedative medications should only be used to achieve the prescribed sedation target, and only after measures to control pain and delirium have been initiated. For patients receiving neuromuscular blocking agents, the level of sedation should be titrated to avoid awareness, as per the treating physician, regardless of the allocation group. After the 36-h intervention period, the sedation strategy for both groups will be at the discretion of the treating physician as needed for clinical care. Reasons for deviations from the allocated sedation target will be recorded. In accordance with guidelines, short-acting sedatives such as propofol should be preferred to benzodiazepines (by either continuous infusion or bolus dosing), but the type and dose of sedatives used to achieve the target RASS will be at the discretion of the treating physician.

Occasionally, patients may have a particular clinical indication for a benzodiazepine-based sedation regimen: for example, complementing very high rates of propofol infusion or marked hemodynamic instability. In such cases, the requirement for continuing benzodiazepine use (vs. an alternative) should be reassessed continuously.

2.5.1 | Continuous deep sedation for 36 h

For patients randomized to continuous sedation, a continuous infusion of a short-acting sedative agent (such as propofol) should be started at randomization to target deep sedation (RASS −4 to −5) and continued until 36 h after randomization. During the first 36 h, this infusion should be increased if the patient becomes rousable, with a RASS target of −4 to −5 until 36 h after randomization. After 36 h, the sedation goal should be according to the treating clinician and continued until the time of liberation from mechanical ventilation, at which time all sedative medications should be discontinued as soon as judged safe.

2.5.2 | Minimal sedation

In patients randomized to minimal sedation, sedative agents shall not be used unless needed for clinical care. During the first few hours of post-cardiac arrest care, patients may require sedation to facilitate safe transfers, imaging, and invasive procedures, but weaning from sedatives should be performed as early as possible, ideally within 6 h of randomization if not at the time of ICU admission. Patients will be continuously assessed for possibilities for extubation immediately after admission to the ICU according to local criteria. If the patient is alert, obeys commands, and is otherwise stable, the patient may be extubated. A patient who does not fulfill criteria for safe extubation should remain intubated and receive minimal sedation as needed for clinical care.

Pain assessment and adequate analgesia are required before providing sedation, which is provided only if analgesia alone is insufficient in ensuring safety in clinical care. If sedation is needed, it should be targeted at the lightest possible level that enables safe treatment and adequate patient comfort. The sedation target should be RASS 0 to −2, unless there is a clinical indication for deeper sedation, in which case a deeper sedation target is acceptable. Although anti-seizure medications should be the primary treatment of refractory status epilepticus and myoclonus, deeper sedation may be used in the minimal sedation arm when necessary to manage clinical situations such as refractory status epilepticus, myoclonus, severe hypoxemia, or confirmed or suspected raised intracranial pressure.

2.6 | Changing sedation

The clinical situation may require continuous sedation to be started in a patient in the minimal sedation group. This is at the discretion of the treating physician. If continuous sedation is started within the first 36 h, the reason for this will be recorded and classified as follows:

Was continuous sedation started within 36 h of randomization?

- No
- Yes—to facilitate general intensive care
- Yes—for seizures

2.7 | Shivering

Shivering will be recorded according to the bedside shivering assessment scale (BSAS) on Day 1–3.[35] The treatment goal for shivering will be to maintain a BSAS score of 0 or 1. To ensure adequate control of shivering, local protocols should be followed. Interventions to minimize shivering will be decided by the treating clinician but might include paracetamol, magnesium, buspirone, increased sedation, and administration of a non-depolarizing neuromuscular blocking agent.

2.8 | General Intensive care

General intensive care, including management of respiration, metabolic disturbances, ulcer prophylaxis, deep venous thrombosis prophylaxis, and other aspects of intensive care, should be delivered similarly in all allocation groups and according to local protocols at the discretion of the treating physicians. Cardiac interventions will also be guided by local protocols. However, participating centers will need to have access to around-the-clock invasive management, either on-site or at a nearby hospital, which is also part of the trial. Cardiac catheterization (coronary angiography) should not be delayed by the trial interventions. Apart from the interventions, adhering to international and national guidelines for post-resuscitation care is recommended.

2.9 | Blinding

The clinical team responsible for the immediate care of the participant will not be blinded to the study interventions due to the inherent difficulty in blinding the interventions (sedation, temperature, and arterial blood pressure). Measures will be taken to ensure that allocation information will only be disseminated within the immediate group of health care workers responsible for patient care. A blinded physician will make a first prognostic evaluation of the participant 72 h after randomization and make a statement on neurological prognosis (for details, see below).

Participants, their legal representatives, and family will only be informed that the patient has been part of the trial but not the allocation group. The outcome assessors, prognosticators, statisticians, the data safety monitoring committee (DSMC), members of the steering committee, and authors of the manuscript will be blinded to treatment allocation. The intervention groups will be coded as "X" and "Y" Two abstracts will be prepared, one assuming X is the experimental group

and Y is the control group—and one assuming the opposite. The author group must approve conclusions before the randomization code is broken.

2.10 | Prognostication and withdrawal of life-sustaining therapies

The SED-CARE trial will employ a conservative and strict protocol for neurological prognostication according to the European Resuscitation Council (ERC) and European Society of Intensive Care Medicine (ESICM) recommendations (see supplement).[6,36] Prognostication will be performed on all participants who are not awake and obeying verbal commands and who are still in the ICU at 72 h after randomization. Prognostication must be sufficiently delayed, ensuring that any lingering effects of sedative agents will not affect the assessment. Prognostication will be made by a physician experienced in neuroprognostication after cardiac arrest, blinded to treatment allocations. The blinded external physician will not make specific recommendations about the withdrawal of life-sustaining measures.

Presumed poor functional outcome will not justify the withdrawal of life-sustaining therapies (WLST) prior to prognostication. Life-sustaining therapies may only be withdrawn before protocolized prognostication in the following situations: if information on a pre-existing advanced care directive or an advanced medical comorbidity (e.g., generalized malignant disease) that prohibits continuation of care becomes available after inclusion in the trial, or if continuation of care is considered unethical due to irreversible multi-organ failure. Brain death, established according to local legislation, will be defined as death and not WLST. See supplemental material for a detailed description of neurological prognostication and WLST.

2.11 | Follow-up

Long-term outcomes will be assessed and recorded during a telephone follow-up at 30 days and during a physical visit or a telephone/virtual meeting 6 months after randomization. The blinded outcome assessor may be an occupational therapist, physician, research nurse, psychologist, or another health care professional. The central follow-up coordinating team will provide outcome assessors with detailed guidelines and study-specific training. More detailed outcomes will be collected in an extended follow-up sub-study at selected sites, including, for example, cognitive function, societal participation, and family impact. This sub-study is described elsewhere.

2.12 | Outcome measures

The primary and secondary outcomes will be assessed 6 months after randomization. The primary outcome will be all-cause mortality. Secondary outcomes will be the proportion of participants with a poor functional outcome defined primarily as a score of 4–6 (moderately severe disability, severe disability or dead) reported by the structured modified Rankin Scale (mRS, range 0–6 with higher scores indicating a worse outcome).[37] If an mRS score cannot be assigned, patients will be categorized based on whether they are dependent on others for basic activities of daily life (need of assistance with, for example, moving indoors, eating, dressing, taking care of personal hygiene), similar to an mRS score of 4–6 but without the detailed information that is needed to separate outcomes between categories. Other secondary outcomes will include the proportion of patients who died or had a predefined serious adverse event in the ICU and patient-reported overall health by using the EQ visual analogue scale (EQ VAS), a part of the EQ-5D.[38]

Exploratory outcomes will be ventilator-free days within the first 30 days, hospital-free days within the first 30 days, mRS (ordinal scale), time-to-event and win ratio (dead versus alive), all steps on the mRS scale, safety event, and detailed information from the EQ-5D-5L.

2.13 | Adverse events

It is recognized that the intensive care patient population will experience several common aberrations in laboratory values, signs, and symptoms due to the severity of the underlying disease and the impact of standard therapies. Intensive care patients will frequently develop life-threatening organ failure(s) unrelated to study interventions, despite optimal management. Therefore, consistent with established practice in academic ICU trials,[39] events that are part of the natural history of the primary disease process or expected complications of critical illness will not be reported as adverse events in this study. All adverse events that are potentially causally related to the study intervention or are otherwise of concern in the investigator's judgment will be reported and reviewed by the management committee and DSMC. A number of specified serious adverse events (SAEs) (as described below) are captured in the trial case report form and will not be separately reported as SAEs.

Only predefined SAEs (Table 1) and any unexpected SAEs will be reported by the investigator to avoid overreporting and to maximize

TABLE 1 Definition of specific serious adverse events.

Serious adverse event	Definition
Sepsis or septic shock	Sepsis-3 criteria[40]
Arrhythmia requiring defibrillation, cardioversion or chest compressions	Arrhythmia requiring defibrillation, cardioversion or chest compressions
Venous thromboembolism	Venous thromboembolism confirmed by imaging. Thrombi related to intravascular cooling devices should be classified as deep vein thrombosis
Moderate or severe bleeding	GUSTO criteria (global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries)[41]
Reintubation	
Non-planned extubation	

the probability of finding true and important differences. We predefined SAEsbased on known and plausible harms of sedation management.

2.14 | Rationale for chosen outcomes

All-cause mortality was chosen as the primary outcome to ensure an unbiased assessment and avoid competing risks. We will use the mRS scale to evaluate functional outcome.[42] The mRS scale is increasingly used in cardiac arrest research and is currently recommended by the Core Outcome Set for Cardiac Arrest (COSCA) and the International Liaison Committee on Resuscitation (ILCOR) consensus statement for measuring functional outcome after cardiac arrest.[37] The primary analysis will be a binary analysis, with the mRS dichotomized to 0–3 (none to moderate disability) versus 4–6 (severe disability or death), as this dichotomization separates patients that are non-dependent from patients that are dependent on others in basic activities of daily living. This dichotomization is also previously used in cardiac arrest trials.[37,42]

The EuroQol-visual analogue scale (EQ-VAS) included as a part of EQ-5D-5L will be used to measure a patient-reported outcome of overall health status. This instrument was chosen since it is easy to use, has shown evidence to be a valid measure in many situations, and could be used as a proxy report if necessary.[38] We will measure possible harmful effects of the intervention by predefined SAEs that are most common and plausibly related to the intervention. A more detailed description of the rationale for chosen outcomes and the exploratory outcomes is available in the supplement.

2.15 | Factorial design and intervention interactions

Factorial trials have the inherent risk of potential interactions between trial interventions in both physiological and patient-centered outcomes.[43] This trial is conducted under the assumption that there is no interaction between the interventions on the present trial's outcomes. The SED-CARE trial intervention has potential physiological interaction with the temperature and mean arterial pressure intervention of the STEPCARE trial. Targeting deep sedation may cause additional vasodilation and a potential effect on cardiovascular function; consequently, lower blood pressure may therefore affect the achievement of the allocated mean arterial pressure (MAP) target and body temperature. However, previous pilot studies suggest a higher MAP target is achievable in most patients.[44,45] Additionally, sedation may interact with the temperature intervention, as sedative agents such as propofol may promote heat loss through vasodilation and might also directly impair hypothalamic temperature regulation.[46] However, no evidence suggests that this interaction could affect the outcomes being assessed. If higher doses of sedatives/deeper levels of sedation, inotropic/vasopressor support, or external cooling are required because of between-group interactions, differential adverse effects of these interactions are theoretically possible. On the other hand, in the minimal sedation group, some patients who wake up and are extubated early may be discharged from the ICU early, which may affect the duration of the other interventions. The DSMC will monitor the trial during its conduct to identify possible interaction effects on outcomes, focusing on patient safety. For more specific situations of intervention interaction, see Supporting Information S1

2.16 | Co-enrolment in other trials

Study participants may be included in any observational trial that does not affect protocol adherence in the STEPCARE trial. We will assess co-enrolment suggestions based on the Spice-8 co-enrolment guidelines.[47] Unless there are clear conflicts between trial interventions, co-enrolment in other trials will be possible. The STEPCARE management committee will assess co-enrolment on a case-by-case basis.

2.17 | Data collection and management

Individual patient data regarding background characteristics, clinical features, and laboratory results will be obtained from medical records, ambulance services, and relatives. Detailed data, including neurological status, body temperature, blood pressure values, and doses of vasoactive and sedative medications, will be collected. Detailed information on collected data is described in the supplement. Data will be entered into a web-based electronic case report form (eCRF) by site personnel. The software for the eCRFs is provided by Spiral, New Zealand, but the storage server for the trial database will be handled by the trial's coordinating team.

2.18 | Sedation specific data collection

The total cumulative dose of the following medications during the intervention up to 72 h post-randomization will be recorded: noradrenaline, propofol, midazolam, remifentanil, sufentanil, fentanyl, dexmedetomidine, paracetamol/acetaminophen, oxycodone, and morphine. Additionally, data on propofol dose (mg/kg/h), dexmedetomidine dose, noradrenaline dose (mcg/kg/min), and midazolam infusion (yes/no) will be collected every 4 hours during the ICU stay up to 120 h.

2.19 | Sample size and power estimation

The sample size estimation is based on a 60% mortality in the control arm and 54.4% mortality in the intervention arm at 6 months, referring to the results of the TTM1 trial,[48] the TTM2 trial,[49] and the International Cardiac Arrest Registry (INTCAR).[50] To demonstrate a relative risk of 0.91 with 90% power at a significance level of 0.05, 1639 participants are required in each group for a total of 3278

participants. In the TTM2 trial, loss to follow-up was approximately 2%, and we expect a similar loss to follow-up in the STEPCARE trial.[49] Therefore, the sample size was increased by 6.8% to 3500 participants; 1.8% of the increment is considered to account for loss to follow-up and, as a pragmatic choice, 5% is considered to account for possible interactions between interventions on patient-centered outcomes. The sample size calculation corresponds to a relative risk reduction of 9.3% and an absolute risk reduction of 5.6%, which is a clinically relevant and realistic treatment effect. For the secondary outcomes, there is an estimated power of 91% to detect a relative risk reduction of 0.9 for poor outcome (mRS 4–6), a power of >90% to detect a difference of 5 points on the EQ-5D-5L VAS scale, and a power of 91% to detect a relative risk reduction or increase of 10% for the predefined SAEs (Table 1).[51]

2.20 | Statistical analyses

All analyses will be conducted according to the intention-to-treat principle and adjusted for 'site' and the allocated intervention in the two other trials of the factorial STEPCARE trial. Dichotomous outcomes will be presented as proportions of participants with the event, and relative risks with 95% confidence intervals. Continuous data will be presented as means and standard deviations for each group, with 95% confidence intervals for the means of the groups and the differences between the means of the groups. Count data will be presented as means, mean differences, and 95% confidence intervals or medians, interquartile ranges, and 95% confidence intervals depending on the observed distribution. Dichotomous outcomes will be analyzed using a mixed effects generalized linear model, continuous outcomes using a mixed effects linear regression model, and count data using the Wilcoxon test. Mock tables, curves, and graphs presenting characteristics of the participants, sedation depth and motor response results, and separation of sedation level between groups and sedative drugs and dose are provided in the supplement. A detailed statistical analysis plan will be published separately.

2.21 | Subgroup analysis

The following subgroup analyses will be performed:

- Age (< median or ≥median)
- Sex (male/female)
- Bystander cardiopulmonary resuscitation (yes/no)
- Initial rhythm (shockable versus non-shockable)
- Time to ROSC (< median or ≥median)
- Circulatory status on admission (presence or absence of circulatory shock diagnosed by the treating physician)
- Baseline risk of poor functional outcome (Miracle2-score: low risk [0–2], medium *risk* [3-5], and high *risk* [6-10]).[52]
- Presumed cause of cardiac arrest at randomization (cardiac vs. others), and
- Diagnosed with chronic hypertension (yes/no).

2.22 | Sub-studies

The main sub-studies of the STEPCARE trial include a biomarker study, an acute kidney injury study, a neuroprognostic study, intensive care monitoring studies, and an extended follow-up study. Separate protocols will be published for these sub-studies. Additional sub-studies will be presented on the STEPCARE trial webpage (www.stepcare.org) and the protocols for these will be published separately.

2.23 | Ethics and informed consent

Ethics application will seek approval for a delayed written consent process, since the intervention must be regarded as an emergency procedure and must be started as soon as the participants are admitted to hospital. Participants regaining consciousness will be asked for written consent as soon as they are able to make an informed decision. It is of importance that ethical approval contains a request to use data also for deceased participants, to avoid survival bias. The consent process will vary from site to site and will align with local ethical approvals, national laws, and the Declaration of Helsinki.[53]

2.24 | Data and safety monitoring and interim analysis

The Charter for the DSMC of the STEPCARE trial describes the role and function of the DSMC. The primary focus of the DSMC is the monitoring of the safety and efficacy of the interventions and the overall conduct of the trial to guard the interests of the trial participants. The first interim analysis was conducted after the enrollment of 500 participants, with the recommendation from the DSMC to *continue the trial as planned*. The schedule of further interim analyses will be decided by the DSMC, but a minimum of three interim analyses will be conducted. The DSMC will arrange for an independent statistician to conduct a blinded interim analysis. The DSMC can request the unblinding of data if required. The survival and safety parameters are provided for the DSMC for the conduct of the interim analyses. Lan-DeMets group sequential monitoring boundaries will be used as the statistical limit to guide recommendations regarding the early termination of the trial.[54] Interventions of the STEPCARE trial will not be stopped for futility. The DSMC may recommend stopping or pausing the SED-CARE trial, or the entire STEPCARE trial if:

- Group difference in the primary outcome measure is found in the interim analysis according to predefined stopping rules;
- Group difference in SAEs is found in the interim analysis.
- Evidence of an interaction influencing outcomes; or
- Results from other studies show benefits or harms associated with one of the allocation arms.

It is the steering group's decision whether the trial should be stopped.

2.25 | Patient group involvement

We followed the COSCA, developed in collaboration with ILCOR, which involved patient representatives to facilitate the selection of patient-centered outcomes.[37,55] Patient organizations in Sweden and Australia were involved in the design phase of the STEPCARE trial.

2.26 | Trial status and timeline

Randomization began in August 2023 and trial sites have been added gradually. The last 6 months follow-up will be performed presumably during 2026–2027. The results from each intervention and sub-study will be reported separately. The initial publications for each STEPCARE trial will include results of primary and secondary outcomes.

3 | DISCUSSION

The aim of this trial is to investigate the effects of deep sedation compared to minimal sedation on outcomes in resuscitated OHCA patients. By investigating these two approaches, we aim to understand the potential benefits and risks associated with each strategy, including their impact on mortality, functional outcome, the occurrence of serious adverse events, and patient-reported overall health. The findings from this trial have the potential to provide valuable insights in the development of sedation protocols tailored to the needs of cardiac arrest patients, ultimately improving their overall care, outcomes, and optimizing resource utilization. The SED-CARE trial is part of the larger STEPCARE trial, which also investigates the effects of mean arterial pressure and fever treatment with or without a temperature control device on recovery after cardiac arrest in a factorial fashion.

3.1 | Rationale for sedation after resuscitation from cardiac arrest

The implementation of hypothermia and temperature management over 20 years ago has led to the routine provision of sedation in post-cardiac arrest care, with deep sedation commonly used in cardiac arrest trials ever since. However, there are limited data on sedation strategies available to guide clinicians in determining the optimal level of sedation for these patients. Considering the risks of sedation, which may affect circulation and ventilation, as well as its potential benefits and neuroprotective effects is crucial. Furthermore, sedation may interfere with neurological prognostication, confounding the evaluation of consciousness, which could significantly impact patient outcomes through premature withdrawal of treatment based on false pessimistic assessments. Thus, investigating the optimal sedation strategy after cardiac arrest and its effects on post-cardiac arrest care is essential. The results from the SED-CARE trial will contribute to future recommendations on sedation practices and provide evidence for optimizing sedation during post-cardiac arrest care.

3.2 | Potential consequences of this trial

The minimal sedation group in this trial may experience adverse events including anxiety, discomfort, pain, non-planned extubation, and development of post-traumatic stress disorder, potentially contributing to impaired neurological function. On the other hand, the deep sedation group may face consequences such as prolonged mechanical ventilation, immobilization leading to venous thromboembolism, infections causing sepsis, arrhythmias, and possible need for reintubation and prolonged intensive care stay.[20–23] The lingering sedation in the deep sedation group may interfere with neurological prognostication.[25,26] In clinical practice, patients who have experienced cardiac arrest are often managed with deep sedation, similar to the deep sedation group in this trial, while those in the minimal sedation group will be managed like any non-cardiac arrest ICU patient. Data will be collected to gain a better understanding of these outcomes throughout the trial.

3.3 | Strengths and limitations

Strengths of the SED-CARE trial include its large sample size, the broad inclusion criteria, and the predefined detailed methodology leading to results with a low risk of bias. The sample size enables detection of small relative risk reductions and comparisons between a variety of cardiac arrest patient subpopulations that may benefit from different sedation targets. Our choice of patient-centered outcomes, together with the blinding of outcome assessors, prognosticators, the steering group, author group, statisticians, and the trial coordinating team, represents significant strengths.

Interactions between the blood pressure, sedation, and temperature strategies, with an effect on patient-centered outcomes, are a possibility and must be considered a limitation. This risk is implicit in all factorial trials. We have designed the study assuming that there is no interaction on the primary, secondary, and exploratory endpoints with the three strategies. Importantly, it is essential to acknowledge that the focus of this trial lies in investigating the targeted sedation depth and not in the assessed sedation depth. This clarification underscores the independence of the trial's treatment allocations and potential interaction effects. Thus, we will not be able to avoid the risk of interactions between interventions because it is an inherent feature of factorial trials. However, we initially deemed the risk of interactions to be minimal. Following calculation of the sample size, we have allowed for a small increment of the sample size (6.8%) to allow for loss to follow-up and a small interaction effect.

This trial may have a potential weakness in this context, as we include severe critical illness and severely brain-injured adult critically ill patients admitted to the ICU. As a result, both groups of patients may have deep sedation scores or scores close to deep sedation on the RASS regardless of sedatives administered, making the distinction between the groups less clear due to the severity of illness and brain injury. Additionally, patients with seizures or temperature control devices started in minimal sedation may need increased sedation, also making the separation between groups less clear. This limitation could impact the trial's ability to detect a difference in outcomes, leaving the question unanswered. However, it is important to distinguish that the aim of this trial is to investigate the intervention of targeted sedation levels. To mitigate these challenges, we plan to conduct sensitivity analyses to explore subgroups of patients that may be affected by these possible confounders.

Having open-label sedation targets is another limitation in this trial. However, measures have been taken to minimize their possible impact on the results and strategies to ensure that we are kept blinded, by blinding the steering group, authors of the manuscript, outcome assessors, prognosticators, statisticians, and the DSMC.

4 | CONCLUSION

The SED-CARE trial aims to investigate if continuous deep sedation for 36 h confers a benefit compared to minimal sedation after cardiac arrest on six-month mortality in adults who are comatose following resuscitation from out-ofof-hospital cardiac arrest. This trial aims for a large sample size and will investigate sedation targets in a broad population of cardiac arrest patients. We anticipate that results from this trial will guide future recommendations on sedation management after cardiac arrest. The SED-CARE trial is part of the large international factorial STEPCARE trial that will also investigate the blood pressure targets and fever treatment after cardiac arrest.

AUTHOR CONTRIBUTIONS

A. Ceric drafted the manuscript. All other authors contributed to the study design and critically revised the manuscript. All authors approved the final version.

AFFILIATIONS

[1]Anesthesia and Intensive Care, Department of Clinical Sciences, Lund University, Skane University Hospital, Malmö, Sweden
[2]Department of Clinical Sciences Lund, Section of Cardiology, Skåne University Hospital, Malmö, Sweden
[3]Faculty of Medicine and Health Technology, Tampere University Hospital, Wellbeing Services County of Pirkanmaa and Tampere University, Tampere, Finland
[4]Intensive Care Unit, Wellington Hospital, Wellington, New Zealand
[5]Medical Research Institute of New Zealand, Wellington, New Zealand
[6]Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Victoria, Australia
[7]Department of Critical Care, University of Melbourne, Melbourne, Victoria, Australia
[8]Department of Anaesthesia and Intensive Care, Helsinki University Hospital and University of Helsinki, Helsinki, Finland
[9]The George Institute for Global Health, Sydney, Australia
[10]Royal North Shore Hospital, Sydney, Australia
[11]Critical Care Program, The George Institute for Global Health, UNSW, Sydney, Australia
[12]Malcolm Fisher Department of Intensive Care, Royal North Shore Hospital, St Leonards, Australia
[13]Critical Care Division and Department of Intensive Care Medicine, The George Institute for Global Health and St George Hospital Clinical School, University of New South Wales, Sydney, Australia
[14]Department of Clinical Sciences Lund, Lund University, Lund, Sweden
[15]Department of Research, Development, Education and Innovation, Skåne University Hospital, Lund, Sweden
[16]Neurology, Department of Clinical Sciences Lund, Lund University, Lund, Sweden
[17]Department of Neurology, Skåne University Hospital, Lund, Sweden
[18]Department of Neurology and Rehabilitation, Skåne University Hospital, Lund, Sweden
[19]Department of Neurology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland
[20]Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland
[21]Department of Anaesthesiology and Intensive Care, Kuopio University Hospital, Kuopio, Finland
[22]Department of Clinical Sciences Lund, Anesthesia and Intensive Care, Lund University, Lund, Sweden
[23]Department of Anesthesia and Intensive Care, Helsingborg Hospital, Helsingborg, Sweden
[24]Copenhagen Trial Unit, Centre for Clinical Intervention Research, The Capital Region, Copenhagen University Hospital—Rigshospitalet, Copenhagen, Denmark
[25]Department of Regional Health Research, The Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark
[26]Adult Critical Care, University Hospital of Wales, Cardiff, UK
[27]Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast, Belfast, UK
[28]Regional Intensive care Unit, Royal Victoria Hospital, Belfast, United Kingdom
[29]University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK
[30]Essex Cardiothoracic Centre, MSE NHSFT, Essex, UK
[31]Anglia Ruskin School of Medicine & MTRC, ARU, Chelmsford, Essex, United Kingdom
[32]Department of Critical Care, Guy's and St Thomas NHS Foundation Trust, London, UK
[33]Faculty of Life, Sciences and Medicine, King's College, Intensive Care Medicine, Centre for Human and Applied Physiological Sciences, School of Basic and Medical Biosciences, London, UK
[34]Intensive Care Medicine, King's Critical Care, King's College Hospital, NHS Foundation Trust, London, UK

[35]Department of Pharmacy and Adult Critical Care, Guy's and St Thomas' NHS Foundation Trust, London, UK
[36]Institute of Pharmaceutical Sciences, School of Cancer & Pharmaceutical Sciences, King's College London, London, UK
[37]Critical Care, University Hospital of Wales, Cardiff, UK
[38]BartsHealth NHS Trust, London, UK
[39]Department of Critical Care, Portsmouth University Hospitals Trust, Portsmouth, UK
[40]Leeds Teaching Hospitals NHS Trust, Leeds, UK
[41]Department of Clinical Sciences, Anesthesia and Intensive Care, Lund University, Skåne University Hospital, Malmö, Sweden
[42]Anesthesia and Intensive Care, Department of Clinical Sciences Lund, Lund University, Skane University Hospital, Lund, Sweden
[43]Department of Anaesthesiology and Intensive Care, Helsingborg Hospital, Helsingborg, Sweden
[44]Department of Operation and Intensive Care, Hallands Hospital, Halmstad, Sweden
[45]Department of Intensive and Perioperative Care, Skåne University Hospital, Lund University, Lund, Sweden
[46]Department of Anaesthesiology and Intensive Care Medicine, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[47]Perioperative Medicine and Intensive Care (PMI), Karolinska University Hospital, Stockholm, Sweden
[48]Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden
[49]Function Perioperative Medicine and Intensive Care, Karolinska University Hospital, Stockholm, Sweden
[50]Department of Clinical Science, Interventionand Technology, Karolinska Institute, Stockholm, Sweden
[51]North Estonia Medical Centre, Tallinn, Estonia
[52]Department of Anesthesia and Intensive Care medicine, Division of Emergencies and Critical care, Oslo University Hospital, Oslo, Norway
[53]Lovisenberg Diaconal University College, Oslo, Norway
[54]Department of Intensive Care Medicine, Stavanger University Hospital, Stavanger, Norway
[55]Department of Anaesthesia and Intensive Care Medicine, Centre Hospitalier de Luxembourg, Luxembourg, Luxembourg
[56]Department of Life Sciences and Medicine, Faculty of Science, Technology and Medicine, University of Luxembourg, Esch-sur Alzette, Luxembourg
[57]University Heart Center Lübeck, University Hospital Schleswig-Holstein, Schleswig-Holstein, Germany
[58]German Center for Cardiovascular Research (DZHK), Hamburg/Lübeck/Kiel, Germany
[59]Department of Neurology and Stroke, University Hospital Tuebingen, Hertie Institute of Clinical Brain Research, Tuebingen, Germany
[60]Charité—Universitätsmedizin Berlin, Department of Neurology, Freie Universität and Humboldt-Universität zu Berlin, Berlin, Germany
[61]Department of Nephrology and Medical Intensive Care, Charité—Universitaetsmedizin Berlin, Berlin, Germany
[62]Department of Intensive Care Medicine, Ghent University Hospital, Ghent, Belgium
[63]Department of Cardiology, Ziekenhuis Oost-, Genk, Limburg, Belgium
[64]University College Dublin Clinical Research Centre at St Vincent's University Hospital, University College Dublin, Dublin, Ireland
[65]The Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Australia
[66]The Alfred Hospital, Melbourne, Australia
[67]Institute of Intensive Care Medicine University Hospital Zurich, Zurich, Switzerland
[68]Institute of Intensive Care Medicine, University Hospital Zurich, Zurich, Switzerland
[69]Department of Intensive Care Medicine, Inselspital University Hospital Bern, Bern, Switzerland
[70]Klinik für Intensivmedizin, Kantonsspital St. Gallen, St. Gallen, Switzerland
[71]Istituto Cardiocentro Ticino, Lugano, Switzerland
[72]Division of Intensive Care and Emergency Medicine, Department of Internal Medicine, Medical University Insbruck, Innsbruck, Austria
[73]IRCCS Policlinico San Martino, Genova, Italy. Dipartimento di Scienze Chirurgiche Diagnostiche Integrate, University of Genova, Genova, Italy
[74]Anaesthesia and Intensive Care, Pordenone Hospital, Azienda Sanitaria Friuli Occidentale, Pordenone, Italy
[75]First Faculty of Medicine, Charles University in Prague, Institute for Heart Diseases, Prauge, Czech Republic
[76]Second Department of Internal Medicine, Cardiovascular Medicine, General University Hospital, Wroclaw Medical University, Wroclaw, Poland
[77]Second Department of Medicine, Department of Cardiovascular Medicine, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Prague, Czech Republic
[78]King Abdullah International Medical Research Center, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
[79]Department of Anestesia, Critical Care and Pain Medicine, Jaber Alahmad Alsabah Hospital, Kuwait City, Kuwait
[80]Tan Tock Seng Hospital, Singapore, Singapore
[81]Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore
[82]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore
[83]Intensive Care Unit, Liverpool Hospital, South Western Sydney Local Health District, Sydney, New South Wales, Australia
[84]South Western Clinical School, University of New South Wales, Sydney, New South Wales, Australia
[85]The Ingham Institute for Applied Medical Research, Sydney, New South Wales, Australia
[86]Liverpool Hospital, Liverpool, Australia
[87]Medical School, University of Queensland, Level 9, Health Sciences Building, Royal Brisbane and Women's Hospital, Brisbane, Australia
[88]The George Institute for Global Health, Faculty of Medicine, University of New South Wales, Sydney, Australia
[89]Department of Clinical Medicine, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, Australia
[90]Critical Care Program, The George Institute for Global Health. Malcolm Fisher Depratment of Intensive Care Medicine, Royal North

Shore Hospital. Northern Clinical School, Sydney Medical School, University of Sydney, Sydney, Australia
[91]Caboolture and Royal Brisbane and Women's Hospitals, Metro North Hospital and Health Service, Brisbane, Queensland, Australia
[92]School of Clinical Medicine, Queensland University of Technology, Brisbane, Queensland, Australia
[93]Critical Care Division, The George Institute for Global Health, University of New South Wales, Sydney, New South Wales, Australia
[94]Middlemore Hospital, Auckland, New Zealand
[95]Department of Intensive Care, Christchurch Hospital, Christchurch Central City, New Zealand
[96]Intensive Care Unit, Tampere University Hospital, Tampere, Finland
[97]Department of Anaesthesia and Intensive Care, Jorvi Hospital, University Hospital of Helsinki and University of Helsinki, Espoo, Finland
[98]Research Unit of Translational Medicine, Research Group of Anaesthesiology, Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland
[99]OYS Heart, Oulu University Hospital, MRC Oulu and University of Oulu, Oulu, Finland
[100]Anesthesia and Intensive Care, Department of Clinical Sciences Lund, Lund University, Lund, Sweden
[101]Intensive and Perioperative Care, Skåne University Hospital, Malmö, Sweden
[102]Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital—Rigshospitalet, Copenhagen, Denmark
[103]Department of Regional Health Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark

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Research data are not shared.

ORCID

A. Ceric https://orcid.org/0000-0001-6846-5961
V. H. Niemelä https://orcid.org/0009-0009-5048-4801
M. B. Skrifvars https://orcid.org/0000-0002-0341-0262
J. White https://orcid.org/0000-0002-4557-3393
A. Lybeck https://orcid.org/0000-0001-7574-3958
A. Lundin https://orcid.org/0000-0002-6623-6847
P. Druwé https://orcid.org/0000-0001-8776-6591
M. Iten https://orcid.org/0000-0002-0140-2066
M. Nafi https://orcid.org/0000-0003-2733-9103
M. Joannidis https://orcid.org/0000-0002-6996-0881
Y. M. Arabi https://orcid.org/0000-0001-5735-6241
A. Aneman https://orcid.org/0000-0003-2096-5304

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immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med*. 2018;46(9):e825-e873. doi:10.1097/CCM.0000000000003299
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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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About the author

Ameldina Ceric received her medical degree from Lund University, Sweden, in 2019 and was admitted as a PhD student at the same university in 2020. She is currently a resident doctor in anesthesiology and intensive care medicine at Skåne University Hospital in Malmö. Combining clinical practice with ongoing research, she has developed a growing interest in sedation and analgesia management. This dissertation aims to bridge evidence-based medicine with the everyday clinical challenges encountered in intensive care units.

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