Inhaled anaesthesia compared with conventional sedation in post cardiac arrest patients undergoing temperature control: a systematic review and meta-analysis

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Word Count (Document Total): 4074
Word Count (Abstract): 249

Keywords: Volatile anaesthetics, sevoflurane, isoflurane, cardiac arrest, temperature control

Abstract

Introduction

Patients admitted with return of spontaneous circulation (ROSC) following out of hospital cardiac arrest (OHCA) are often sedated to facilitate care. Volatile anaesthetics have been proposed as alternative sedatives because of their rapid offset. We performed a systematic review and meta-analysis comparing the use of volatile anaesthetics to conventional sedation in this population.

Materials

We searched four databases (MEDLINE, Embase, CENTRAL, and Scopus) from inception to January 6, 2022. We included randomized trials and observational studies evaluating patients admitted following ROSC. We pooled data and reported summary estimates using odds ratio (OR) for dichotomous outcomes and mean difference (MD) for continuous outcomes, both with 95% confidence intervals (CIs). We assessed risk of bias using the Newcastle Ottawa Scale and certainty of evidence using GRADE methodology.

Results

Of 1,973 citations, we included three observational studies (n=604 patients). Compared to conventional sedation, volatile agents had an uncertain effect on delirium (OR 0.96, 95% CI 0.68-1.37), survival to discharge (OR 0.66, 95% CI 0.17-2.61), and ICU length of stay (MD 1.59 days fewer, 95% CI 1.17-4.36, all very low certainty). Patients who received volatile anaesthetic underwent a shorter duration of mechanical ventilation (MD 37.32 hours shorter, 95% CI 7.74-66.90), however this was based on low-certainty evidence. No harms were described with use of volatile anesthetics.

Conclusion

Volatile anaesthetics may be associated with a decreased duration of mechanical ventilation in patients admitted with ROSC however this is based on low-certainty evidence. Further data are needed to assess their role in this population.

Introduction

Out-of-hospital cardiac arrest (OHCA) is generally associated with poor prognosis, with as few as 5-10% of patients surviving to hospital discharge (1, 2). Among patients admitted to the intensive care unit (ICU) following return of spontaneous circulation (ROSC), withdrawal of life-sustaining therapy because of prognostication of a poor outcome following hypoxic-ischemic brain injury remains the major cause of death(3). Although effective bystander cardiopulmonary resuscitation (CPR) can improve neurological outcomes(2), many patients will be left with some neurological impairment even if they do survive to hospital discharge.

Patients with ROSC and impaired neurological function following OHCA routinely receive temperature control including normothermic temperature control as part of usual post-arrest care(4, 5). Patients are often sedated to allow time for initial resuscitation, improve tolerance of mechanical ventilation, and minimize cerebral oxygen consumption(6). A combination of intravenous propofol, opioids, and/or benzodiazepines are generally used to achieve sedation targets in these patients, however these medications can rapidly accumulate, leading to prolonged awakening, increased delirium, and challenging neuro-prognostication.

Volatile anaesthetics, such as sevoflurane and isoflurane, have been proposed as alternative sedatives in this population, due to their rapid offset, which may allow earlier opportunities for neurological assessment. (7, 8). Other purported benefits of these agents include decreased cerebral metabolic rate. Several small observational studies have demonstrated feasibility and safety of these agents in the sedation of patients following cardiac arrest. We therefore performed a systematic review and meta-analysis to compare the use of volatile anaesthetics with conventional intravenous sedation in patients admitted with ROSC following OHCA. We hypothesized that the use of volatile anaesthetics will result in no difference in survival, but shorter ICU length of stay and duration of mechanical ventilation.

Methods

We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement guideline(9). The study protocol was registered on *Open Science Framework* on April 19, 2021 (Registration DOI 10.17605/OSF.IO/NA43Z). No institutional ethics approval was required for this project given that it was a systematic review of available literature.

Search Strategy

We searched four databases (MEDLINE, Embase, CENTRAL, and Scopus) from inception to January 6, 2022(10) (see Supplemental File for full search details). We did not apply limits to language or publication date. The main search concepts comprised of terms related to cardiac arrest or temperature control, and inhaled volatile anaesthetics, and was informed by previously conducted systematic searches(11-17). We exported results to Covidence (Melbourne, Australia) and eliminated duplicates.

Study Selection

Two independent reviewers (SP, MFL) screened all titles and abstracts. Full texts of eligible studies from titles and abstract screening were evaluated by two independent reviewers (SP, MFL) and assessed based on eligibility criteria. All conflicts were resolved by a third independent reviewer (RM).

We intended to include retrospective or prospective observational studies, as long as they had a control cohort, as well as randomized controlled trials. We excluded case reports, case series and narrative reviews. We included studies that met the following criteria: 1) Evaluated adult patients (≥ 18 years); 2) evaluated patients who have had an out of hospital cardiac arrest and have achieved ROSC; 3) evaluated patients undergoing TTM following ROSC; 4) compared the use of at least one volatile inhaled anaesthetic versus conventional intravenous sedation; and 5) evaluated one of our outcomes of interest.

Outcomes and Analysis

We included the following outcomes of interest: Presence of delirium (within 14 days of ROSC and diagnosed using the Confusion Assessment Method for the ICU [CAM-ICU] score), survival to hospital discharge, ICU and hospital length of stay, duration of invasive mechanical ventilation, need for tracheostomy, ventilator-associated pneumonia (VAP), vasoactive-inotrope score (VIS) during the ICU admission, renal replacement therapy (RRT), and neurological outcome at the time of hospital discharge (based on the Modified Rankin Scale (mRS)). We reported pooled outcomes if at least two studies reported on them.

We used DerSimionian and Laird random effects models to conduct meta-analysis using RevMan Version 5.3 (The Cochrane Collaboration, 2020). We planned to separately pool RCT and observational data but did not find any eligible RCTs. We expressed categorical data as numbers and percentages and continuous variables as means (SDs) for normally distributed variables. Study weights were generated using the inverse variance method. We present results as odds ratio (OR) for dichotomous outcomes and mean difference (MD) for continuous outcomes, both with 95% confidence intervals (CIs). For continuous outcomes, data presented as medians with interquartile range were converted to means with standard deviation using a published algorithm(18) prior to performing meta-analysis. For observational studies, we preferentially used adjusted effect estimates from individual studies, if provided. If not, we used unadjusted estimates. In situations where we used adjusted estimates, we also performed sensitivity analysis using unadjusted estimates when this data was available. We assessed for statistical heterogeneity between studies using the Chi-squared test for homogeneity, the I-squared statistic, and visual inspection of the forest plots. We did not perform any subgroup analysis.

Assessment of Risk of Bias

Two reviewers (SP and MFL) independently assessed the risk of bias of included studies using the Newcastle Ottawa Scale (NOS)(19). We resolved all disagreements by consensus. We defined cohort studies to have a low risk of bias based on NOS when they scored 3 or greater on selection, 1 or greater on comparability, and 2 or greater on outcome/exposure domains.

Assessment of Certainty of Evidence

We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework to assess certainty of evidence for each outcome, addressing the domains of risk of bias, imprecision, inconsistency, indirectness, and publication bias(20).

Results

Of 1,978 citations identified by the search, we reviewed 17 full-text articles and included 3 eligible retrospective cohort studies (Figure 1) (21-23). Two studies (21, 23) presented propensity score matched (PSM) data and the third (22) presented unadjusted data. Of the included studies, one (n=85) evaluated sevoflurane and two (n=146) evaluated isoflurane. In terms of comparator, one (n=178) used propofol as the primary sedative and sufentanil as the secondary agent, one (n=46) used propofol and midazolam, and one (n=110) used fentanyl and midazolam. On average, 72.7% of patients were male, and 59.3% presented with a shockable rhythm. All patients received temperature control for a total of 24 hours, and the target temperature ranged from 33 to 36 degrees Celsius. Median time to ROSC ranged from 12 to 29.1 minutes in patients treated with conventional sedation, and 12 to 30.6 minutes in patients treated with volatile anaesthetics.

Supplemental table 3 displays risk of bias in included studies. Only one of three included studies was identified as high-risk for bias based on our pre-defined criteria.

Compared with conventional intravenous sedation, use of volatile anaesthetics had an uncertain effect on presence of delirium (OR 0.96, 95% CI 0.68 to 1.37), survival to hospital discharge (OR 0.66, 95% CI 0.17 to 2.61), time to discharge from ICU (MD 1.59 days fewer, 95% CI 4.36 days fewer to 1.17 days longer), and time to discharge from hospital (MD 0.96 days fewer, 95 CI 7.02 days fewer to 5.1 days longer); (all very low certainty) (Figure 2, Supplemental Table 4). Patients who received volatile anaesthetic had a shorter duration of mechanical ventilation (MD 37.32 hours shorter, 95% CI 7.74

to 66.90 hours fewer), however this was based on low certainty evidence. None of the other outcomes were reported in more than one study.

Sensitivity analysis using unadjusted estimates (see Supplemental Figure 5) for the duration of mechanical ventilation outcome did not change the results or conclusions.

Discussion

In this systematic review and meta-analysis comparing the use of volatile anaesthetics with conventional sedation in patients admitted with ROSC following OHCA and undergoing TTM, we found an uncertain effect with volatile anaesthetic use on presence of delirium, survival to hospital discharge, time to discharge from ICU, and time to discharge from hospital. The very low certainty evidence was because the data were observational and there were very few published studies. Nonetheless, use of volatile anaesthetics may reduce the duration of mechanical ventilation, however this was based on low certainty evidence. The most important finding of our analysis was a lack of robust data surrounding use of volatile anesthetics in this population, and a need for further studies before definitive conclusions can be made regarding their use for this indication.

The recent TTM-2 trial demonstrated no difference in outcomes when temperature control with a target of 33^{o}C was compared with normothermic temperature control in patients admitted following OHCA (24), adding to the increasing data suggesting routine use of mild hypothermia confers no benefit to patients admitted following ROSC, and may cause harm(4). A shift towards fever prevention instead of mild hypothermia was highlighted in the most recent iteration of the European Resuscitation Council's guidelines on temperature control following cardiac arrest(5, 6). Despite this finding, sedation remains an essential component of post-resuscitation care for most patients admitted following ROSC. As the standard of care moves away from hypothermic temperature control, focusing instead on avoidance of fever, it may be possible to wean sedation more rapidly, enabling earlier neuro-prognostication. This further highlights the potential role that a short-acting sedation strategy can play in this cohort of critically ill patients. Current guidelines highlight the uncertainty regarding an optimal sedation strategy for patients following OHCA due to a paucity of evidence, and no recommendation can be made about the use of volatile anesthetics because outcome data are lacking(6).

Although there are very few data on the use of volatile anesthetics in patients following ROSC, our findings are similar to those found in other patient populations. The trend of shortened time to extubation has been observed with the use of volatile anesthetics compared to conventional intravenous sedation in three systematic reviews of critically ill adults in the ICU (25-27). Similarly, three randomized trials examining volatile anesthetics in patients admitted to the ICU following cardiac surgery with cardiopulmonary bypass demonstrated shortened time to extubation with the use of volatile agents(28-30) with no difference in length of ICU stay. These findings were again demonstrated in a systematic review and meta-analysis of eight randomized trials examining a similar post-operative population(31). In this review, as was observed in our analysis, there was no difference seen in time to discharge from ICU, time to discharge from hospital, or rate of in-hospital death with the use of volatile anaesthetics. Importantly, these populations differ significantly from the OHCA population, however this trend remains an interesting observation.

Several factors may limit the use of volatile anaesthetics for sedation in the critical care population. First, use of volatile anaesthetics outside of the operating room requires specialized delivery systems and thorough education of clinicians and staff, which may be costly(32, 33). Volatile anesthetics are also known to cause post-operative nausea and vomiting(34), however this is primarily a concern when dispensed at doses typically used for intraoperative anesthesia. Lastly, significant environmental concerns exist regarding the use of volatile anesthetics which may limit their future role as a method for sedation in the ICU (35, 36), however this impact could be mitigated with the use of a scavenging system(37, 38).

This analysis carries important strengths and limitations that should be acknowledged. There is scarce evidence examining use of volatile anesthetics compared to intravenous sedation in patients admitted following ROSC, and this meta-analysis is an important first step towards understanding their role for sedation in this population. We used a robust search strategy and evaluated certainty of effect estimates for each outcome using GRADE. However, we are unable to draw significant conclusions regarding their role in this population due to very low or low certainty evidence. All three of our included studies were observational as no randomized or prospective trials exist studying this intervention. We observed significant clinical heterogeneity across the included study populations that limits generalizability, although this did not necessarily translate into statistical heterogeneity in our analysis. There also was variability in choice of both volatile and conventional sedation agents across studies, which is an important consideration given that experimental models of cardiac arrest have shown differing neurological outcomes with the use of various intravenous sedation agents(39) as well as different volatile agents(40). Two of our papers (22, 23) included propofol as the primary conventional sedation agent, whereas the analysis by *Krannich et al* (21) used a combination of fentanyl and midazolam– which both have significantly longer offset time than propofol. Interpretation of the analysis by *Foudraine et al* (23) is challenged by the fact that the conventional and volatile sedation groups were cooled to different target temperatures (33°C and 36°C, respectfully). Furthermore, the survival observed in all three studies was higher than that typically reported in the literature (2, 24). Also, our outcomes were strictly clinical, and we were therefore unable to evaluate potential effects that volatile anesthetics had on the brain at the cellular level. Lastly, we did not consider other potential confounding variables in our analysis that may have affected sedation strategies, including other medications used at the time TTM, as well as the use of TTM itself, which can affect the pharmacokinetics of intravenous sedation medications(41).

Due to the scarce data that exist evaluating volatile anaesthesia in this population, further data, both observational and randomized, are needed to clarify its feasibility, safety, and efficacy.

Conclusions

Volatile anaesthetics may be associated with reduced duration of mechanical ventilation in patients admitted with ROSC following OHCA however this is based on low certainty evidence. Further data, including randomized controlled trials, are needed to further assess their role in this population.

Conflicts of Interest

JPN is Editor-in-Chief of *Resuscitation.* No other authors have any conflicts of interest to declare.

Acknowledgements

The authors would like to thank Valentina Ly, MLIS (Health Sciences Library, University of Ottawa) for peer review of the MEDLINE search strategy.

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Figure Legends:

Figure 1: Flowchart summarizing literature search and study selection

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Figure 2: Meta-analysis of outcomes of interest

Figure 2: Meta-analysis comparing presence of delirium (A), survival to discharge (B), length of ICU stay (C, days), length of time receiving mechanical ventilation (D, hours), and length of time to hospital discharge (E, days).