EGYPTIAN JOURNAL OF ANAESTHESIA
2019, VOL. 35, NO. 1, 77–85
https://doi.org/10.1080/11101849.2019.1673535

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

Daily sedation interruption versus routine sedation in critically ill children: A systematic review and meta-analysis

Mona A. Azzam[a], Enas F. Elngar[a], Shimaa a Al- Touny[b], Amna T. Shaffik[c], Mohammad H. Hussein[d], Khalid A. Sabahy[e] and Ghada A. Kamhawy[b]

[a]Department of Pediatrics, Suez Canal University, Ismailia, Egypt; [b]Department of Anesthesia, Suez Canal University, Ismailia, Egypt; [c]Faculty of Pharmacy, Suez Canal University, Ismailia, Egypt; [d]Ministry of Health, Cairo, Egypt; [e]Faculty of Medicine, Suez Canal University, Ismailia, Egypt

ABSTRACT

Background: Strategies aiming lighter sedation have demonstrated promising results in adults. This review was designed to evaluate the efficacy and safety of daily sedation interruption (DSI) versus sedation protocols in mechanically ventilated children.

Methods: This was a systematic review and meta-analysis. We searched MEDLINE, Scopus, Cochrane Library and Web of Science from 1980 to August 2018 for randomized control trials comparing the two forms of sedation in question, with outcomes that included duration of mechanical ventilation, length of stay in the pediatric intensive care unit, total midazolam doses and adverse events.

Results: Three studies were included in the review and meta-analysis after fulfilling the inclusion criteria. One was a multicenter trial and two were single-center trials, with a total of 261 patients. There was a shorter duration of both mechanical ventilation and intensive care stay, but with marked heterogeneity. All the results were in favor of DSI except adverse events which were higher in the DSI group.

Conclusion: On comparison of DSI to routine sedation, we found evidence of benefit as regards, duration of mechanical ventilation, length of intensive care unit stay and midazolam doses. However, there was some evidence of harm with more adverse events.

ARTICLE HISTORY
Received 11 July 2019
Revised 6 September 2019
Accepted 22 September 2019

KEYWORDS
Sedation; pediatric; mechanical ventilation; interruption

1. Introduction

Many critical children admitted in the pediatric intensive care unit (PICU) are subjected to life-support technologies, with the most common being invasive mechanical ventilation. Because of the associated pain and discomfort, sedation is necessary, despite confirmation of many adverse consequences on mobilization, cognition, and psychological health, including post-traumatic stress disorder [1].

Ideally, optimal sedation is tailored for every patient. However, there are many obstacles to being able to achieve this, including encephalopathy related to the primary disease, organ dysfunction affecting drug metabolism, and drug–drug interactions. An ideal drug would have the following features: minimal interactions with other drugs, low bioaccumulation, dose adjustability,and negligible adverse effects. As there are no sedative agents that satisfy these criteria for critically ill children, alternative strategies may be employed to minimize drug bioaccumulation and subsequent oversedation and the ensuing side effects. These protocols may involve maintaining lighter sedation levels or interrupting sedation to avoid the potentially deleterious effects of sedation [2]. However, these strategies are not backed with sufficient evidence, with controversy as to which approach is more effective [3].

Such strategies include the use of intermittent boluses instead of continuous administration, selection of sedatives with ultra-short therapeutic half-lives, and daily sedation interruption (DSI) [4]. The definition of DSI is a temporary interruption or hold of intravenous sedation. This may apply to fixed dose bolus or continuous infusions and is useful in minimizing drug bioaccumulation, allowing patients to be more awake, facilitating neurological assessment, and evaluating effects of drug discontinuation. As with many interventions, there are more studies conducted on adults than children. In the last few years, the safety and efficacy of DSI has been demonstrated in some studies [5,6], while other studies could not find a statistically or clinically significant effect of DSI on outcome [7–9]. DSI had become a routine practice in adult intensive care units (ICUs) based on earlier studies such as Mehta et al. [5]. However, that study (from nearly a decade ago) was refuted by the Mehta 2012 study [7] that showed no evidence of benefit to DSI when compared to protocolized sedation targeting a light level of sedation.

CONTACT Ghada A. Kamhawy gkamhawy@yahoo.com Department of Anesthesia, Suez Canal University, Ismailia, Egypt

This work was conducted at the Faculty of Medicine, Suez Canal University, Egypt.This article has not been published in any form and is not being considered for publication in any other journal.

For critically ill children, the effectiveness and safety of DSI has not been established. Adult data cannot be generalized to the pediatric population and there is a paucity of studies addressing this important gap in the literature. There are fewer studies on children, and with conflicting results. DSI and continuous sedation have been compared in mechanically ventilated children [10]. The authors found a better outcome with DSI, with the length of mechanical ventilation and duration of intensive care stay significantly reduced in the interrupted sedation group (10.3 vs 7.1 days, p = 0.021 and 14.1 vs 10.07 days, p = 0.002, respectively), with no significantly different adverse event rate. Taking into consideration the variation in patient population and ICU practices between the two settings, these results needed further validation. In a Dutch multicenter study, efficacy and safety of daily interruption of sedation in critically ill children were investigated [11]. Alarmingly, not only did they find a lack of improvement with DSI, they also reported unexpected deaths. Other studies have also evaluated DSI, with variable results. The objective of this study was to systematically review studies that compared two approaches: daily sedation interruption versus routine sedation protocols.

2. Materials and methods

2.1. Search strategy

We searched Medline, Scopus, Cochrane Library and Web of Science for systematic reviews and randomized control trials (RCTs) by combining the following keywords: ("daily interruption") And ("sedatives" OR "sedation") And ("intensive care" OR "critical care" OR "critically ill") AND ("children" OR "pediatric"). Only English references were chosen. We searched only RCTs conducted on children from 1980 to August 2018 that compared DSI with routine sedation, also occasionally called protocolized sedation (PS). References were organized in Abstrackr citation screening program where full-texts of the potentially relevant articles were assessed independently to determine the included studies. Any disagreements between authors were resolved by consensus. Prior to initiation of the study, the systematic review was registered in the PROSPERO database (CRD42017071477).

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used for the review and reporting of the methods and results in this study [12].

2.2. Study selection

Studies were included if they included children on sedation and invasive mechanical ventilation within a PICU setting. We then checked for those that compared DSI with a predefined sedation protocol and assessed any of the outcomes we were interested in.

2.3. Data extraction

A data extraction table from a RevMan file was prepared. The data were extracted and crosschecked for accuracy with the original publications. Errors were corrected where necessary. Full-text articles were obtained and were reviewed independently by three reviewers to determine final eligibility.

Each author extracted independently the details of each RCT using the predesigned form that include: site, study design details, number of participants, PS and DSI details, year of publication, and the outcomes. Our primary outcomes were duration of mechanical ventilation and length of stay in the PICU. We also extracted data for out secondary outcomes: adverse event frequency and total dose of sedatives.

2.4. Risk of bias assessment

This was performed using the Cochrane risk of bias assessment tool for clinical studies [13]. The studies were categorized as "low", "uncertain" or "high" for all criteria, which included randomization technique, concealment of allocation, technique of blinding of patients, assessors and health care providers, incomplete outcomes, and sources of bias including selective outcome reporting. The lack of agreement was resolved by consensus. All data regarding any outcome or adverse event were recorded.

2.5. Data analysis

Search results are shown in Figure 1. Comprehensive Meta-Analysis Version 2 was used, and calculation of the I-squared statistic was used to assess heterogeneity. Study details (including total mechanical ventilation duration, length of stay, frequency of adverse events, total dose of sedatives) were summarized Table 1. A random effects model was used to calculate relative risk (RR). In studies where the median (range/interquartile range) was reported, the mean (SD) was calculated from them as mentioned by Wan et al. [14]. Results were considered statistically significant if the p value was less than 0.05.

3. Study characteristics

3.1. Results of the search

A total of 650 references were identified by the search strategies. Studies were included if they included children on sedation and invasive mechanical ventilation within a PICU setting. We then checked for those that compared DSI with a predefined sedation protocol and assessed any of the outcomes we were interested in.

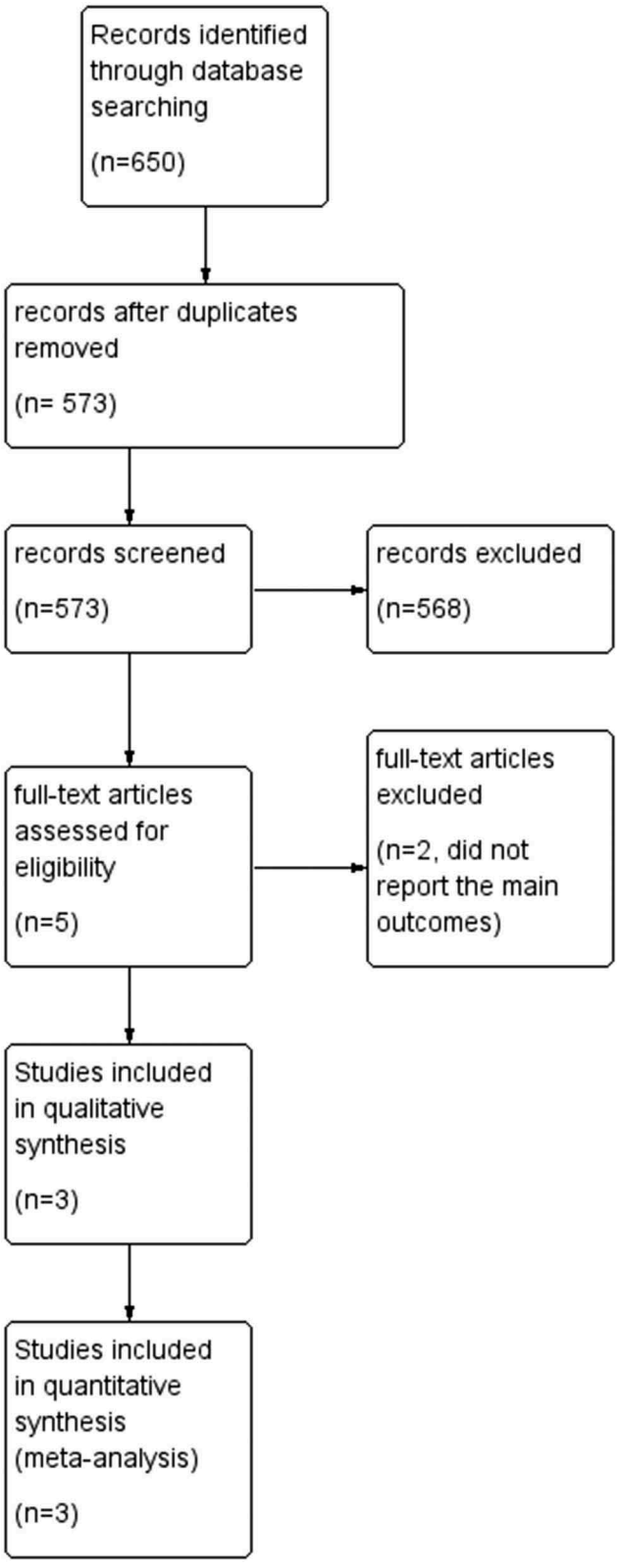

Figure 1. Systematic review study selection process.

We reviewed the abstracts of these studies for eligibility, of which five [10,11,15–17] were retrieved for full-text assessment. Only three of these studies met the inclusion criteria [10,11,15]. The remaining two studies did not include the outcomes of interest [16,17] (Figure 1). This was performed by two independent reviewers to reduce bias and there was 100% agreement rate.

3.2. Included studies

Involved studies characteristics are shown in Table 1. We included three trials comprising 261 participants. In general, the studies were small, with sample sizes ranging from 30 to 129 participants. All of them were published between 2012 and 2016. Only one trial was a multi-centre study, [11] while the others were conducted at a single

Table 1. Characteristics of included studies.

Study	Country	No. of centers	No. of patients (PS/DSI)	Mean age (PS/DSI)	Female (%) (PS/DSI)	Outcomes
Gupta 2012 [10]	India	1	56/46	4.1/3.6	28.6/32.6	1. Total duration of mechanical ventilation 2. Length of ICU stay 3. Days awake on sedative infusions (number) 4. Days awake on sedative infusions (percentage) 5. Frequency of adverse events 6. Total dose of sedatives
Verlaat 2014 [15]	The Netherlands	1	15/15	12.3/5.0	60.0/27.0	1. Total doses for each medication in mg/kg in the first 3 days 2. Number of intermittent bolus administrations during the first 3 days. 3. Near incidents during the entire study period. 4. Duration of mechanical ventilation 5. Length of ICU stay 6. Changes in COMFORT-B score.
Vet 2016 [11]	The Netherlands	3	63/66	Not specified	42.4/34.9	1. Number of ventilator-free days at day 28. 2. Duration of mechanical ventilation. 3. Length of ICU stay. 4. Length of hospital stay. 5. 30-day mortality. 6. Adverse events 7. Total and median dose of sedatives 8. number of COMFORT-B scores 9. Incidence of withdrawal symptoms [SOS scale] 11. Total number of screenings for safety.

pediatric intensive care unit [10,15]. Two trials took place in the Netherlands and one study in India.

All trials reported the duration of mechanical ventilation and length of ICU stay, but there was variability in reporting and dosing of the sedatives. All studies reported using both midazolam and morphine as sedatives. However, Gupta et al. [10] only reported a total dose of midazolam. Verlaat et al. [15] measured only the amount of sedatives in the first 3 days of the study and reported the percentage of change in sedative use after inclusion.

Descriptions of the DSI and the sedation protocols are demonstrated in Table 2.

3.3. Risk of bias assessment

This is illustrated in Table 3.

Generally, most trials had a low risk of bias, with the exception of blinding of participants, healthcare providers or outcome assessors. Random sequence generation was clearly stated in all studies. Allocation was concealed in two trials using central allocation [11] and sealed numbered envelopes [10]. However, allocation concealment was unclear in one study [15]. The nature of the intervention made blinding of participants and clinicians unfeasible. No trial has reported blinding of the outcome assessor; thus the risk of bias was considered unclear in this domain. We found that all studies had complete data and used intention-to-treat bias, therefore with a low risk of attrition bias.

3.4. Outcomes

The total duration of mechanical ventilation was assessed in three studies (n = 261 patients). There was an association between reduction in the duration of mechanical ventilation and DSI in comparison to routine sedation protocols. However, this result was markedly heterogeneous. [Mean difference (MD) = −0.36 days, 95% confidence interval (CI) −0.66 to −0.07 days, P = 0.01, I^2 = 23%] (Figure 2).

ICU lengths of stay were available from all three studies, including 261 patients. Data showed significant reduction in the ICU length of stay between the sedation protocols and daily sedation interruption (MD = −0.36 days, 95% CI −0.67 to −0.05 days, P = 0.02, I^2 = 31%) (Figure 3).

Total adverse events were reported in all three studies. Data demonstrated some difference in overall adverse events between the sedation protocol and daily sedation interruption groups (RR 0.67, 95% CI 0.35 to 1.47, P = 0.32, I^2 = 0%) (Figure 4).

Total dose of midazolam was assessed in two studies as other sedative drug was not available. Results show a significant reduction in the total dose of midazolam in daily sedation interruption groups compared to sedation protocol one (MD = −0.49, 95% CI −0.76 to −0.23 days, P = 0.0002, I^2 = 0%) (Figure 5).

4. Discussion

This systematic review and meta-analysis were performed in an attempt to reach a conclusion regarding sedation in mechanically ventilated children in intensive care units. Critically ill children often receive sedation to facilitate care and reduce discomfort or anxiety. Although patient comfort is maximized by continuous drug administration, this also leads to drug bioaccumulation and the adverse effects of oversedation, hence the concept of DSI.

Of a total of 650 references, only five were fully assessed for eligibility. Two of these were excluded for different designs or outcomes, leaving us with three that met the inclusion criteria, with a total of 261 participants. Although Gupta [10] and Verlaat [15] had similar results, while Vet [11] had some contradictory results, the latter had a larger sample size as it was a multicenter trial and therefore had a larger impact on our results. This is the first systematic review addressing this issue in

Table 2. Sedation protocol and daily interruption performed in each study.

Study	Sedation protocol	Daily sedation interruption
Gupta 2012 [10]	Midazolam was given as a loading dose of 0.1–0.3 mg/kg bolus followed by an infusion ranging from 0.1 to 0.3 mg/kg/hr. This was in combination with morphine at 0.01–0.03 mg/kg/hr.	Sedation was given as per the regular protocol, with a daily interruption of sedative infusion at 8:00 am until the patient became fully awake or too uncomfortable, at which time the infusion was restarted at 50% and titrated.
Verlaat 2014 [15]	Standard sedation was the control group in which midazolam and morphine were given according to clinical judgement with maximum infusion rates of 0.3 mg/kg/hr and 0.03 mg/kg/hr respectively. Level of consciousness was monitored by the COMFORT-B score, and additional sedation was given if agitation or discomfort were noted.	The infusion of sedatives was similar to the control group with daily cessation at 1:00 pm after clinical rounds. Assessments using the COMFORT-B score were performed regularly and any score ≥17 initiated an immediate restart of sedative infusions.
Vet 2016 [11]	After mechanical ventilation for 24 h, patients were assessed for a safety screen daily. If the patient passed the screen, blinded infusions were initiated at the same infusion rates. During blinded infusions, levels of sedation was assessed every bi-hourly via COMFORT-B and NRS scores. When assessments indicated distress, a loading dose of midazolam was given (0.1 mg/kg, intravenously), and titrated to optimize sedation.	Following a safety screen, blinded infusions were initiated, and the level of sedation was assessed as in the control group in the same way as in the PS group. When assessments indicated distress, a loading dose of midazolam was given (0.1 mg/kg, intravenously), and titrated to optimize sedation.

Table 3. Risk of bias assessment of the enrolled studies.

Study	Random sequence generation	Allocation concealment	Blinding of participants and professionals	Blinding of outcome assessors	Incomplete outcomes	Selective outcome reporting	Other sources of bias
Gupta 2012 [10]	Low	Low	High	Unclear	Low	Low	Low
Verlaat 2014 [15]	Low	Unclear	Unclear	Unclear	Low	Low	Low
Vet 2016 [11]	Low	Low	High	Unclear	Low	Low	Low

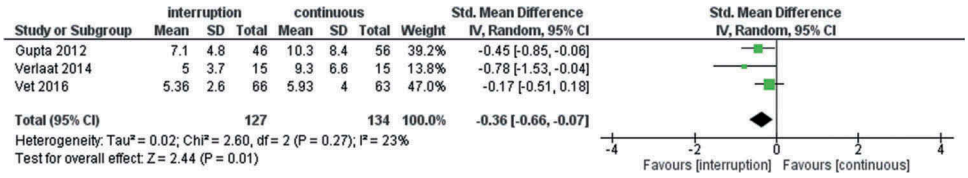

Figure 2. Duration of mechanical ventilation in DSI versus sedation protocols.

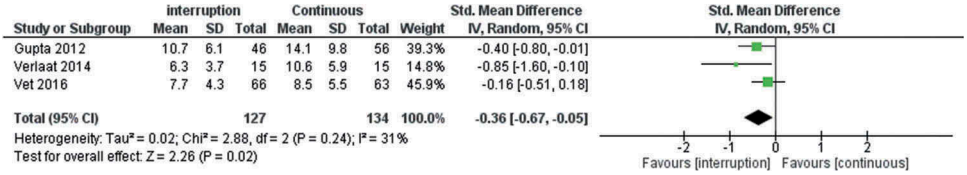

Figure 3. Length of ICU stay in DSI versus sedation protocols.

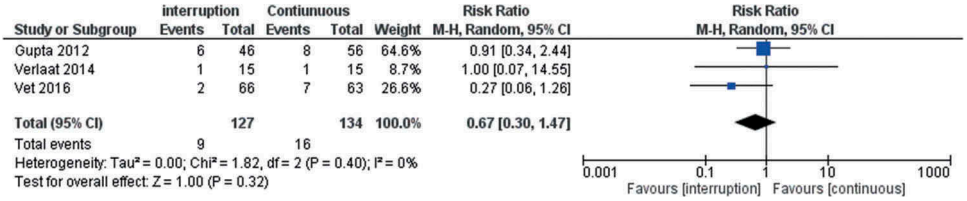

Figure 4. Adverse events in DSI versus sedation protocols.

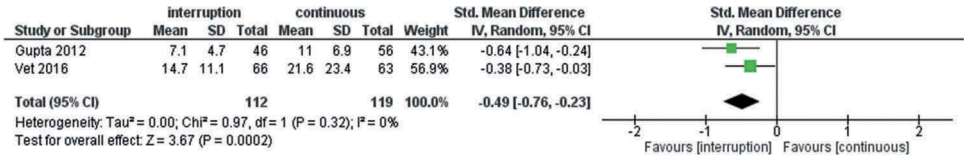

Figure 5. Total dose of midazolam in DSI versus sedation protocols.

children. On comparison to systematic reviews and meta-analyses on use of DSI in adults, Nassar et al. [18] included 5 studies with 241 participants. Similarly, Augustes [8] included five randomized control trials (RCTs) identified but had more participants and used pooled data for 699 patients. The largest systematic review was a Cochrane study, including nine eligible trials with a total of 1282 patients [4].

Although our results did show a statistically significant decreased total duration of mechanical ventilation with daily sedation interruption, there was marked heterogeneity. This may be explained by the conflicting results between Vet et al. [11] on the one hand, and the other two RCTs on the other hand [10,15]. The authors themselves had noted this discrepancy and had explained it by the fact that they had protocolized nurse-driven sedation, which may have a positive effect on minimization of sedation, as previously demonstrated in an adult study [7]. Importantly, this heterogeneity is entirely consistent with the results in Mehta et al. 2012 [7], a huge and important adult study that found that DSI + protocolized sedation was not beneficial when compared to protocolized sedation alone, and in fact was associated with a higher total sedative exposure and a higher nursing workload. Another factor may be that patient characteristics varied between Gupta et al.'s RCT [10] and Vet et al.'s [11], in that a large proportion of the former had neurological illness (70%), whereas the latter excluded such patients. Additionally, the midazolam doses were much higher than commonly used doses. The authors also suggested a paradoxical Hawthorne effect in the

control group, possibly related to close monitoring [19]. In a large RCT including 1225 critically ill pediatric patients, protocolized sedation was compared to usual care and there was no significant effect on duration of mechanical ventilation [16].

A similar heterogeneity was also found in a systematic review for adults, but for this outcome they had actually used the data from only two studies [20]. Even in a larger meta-analysis that conducted a sub-analysis to compare the duration of mechanical ventilation in DSI versus protocolized sedation, no significant difference was found between the two approaches [4].

Our results showed a statistically significant shorter PICU stay, which is agreement with an adult systematic review [20]. Although our CI was smaller than that of the adult study, the mean different was much smaller in our results (0.36 versus 5.05 days), which could be related to the results found in each study as regards the duration of mechanical ventilation (0.36 days in our study versus 6.7).

One of the aims of this systematic review and meta-analysis was to evaluate safety in critically ill children. Using data from all three studies, we found no differences between the two approaches to sedation. This was an important finding as we were particularly concerned with the high mortality reported in one of the RCTs included in our data [11], who had found a 9.1% mortality rate in the DSI group (6 patients) versus 0% in the PS group. The clinical significance of this is doubtful as there was no identifiable causal relationship incriminating DSI within such a short timeframe. This may be an unfortunate coincidence, but it is noteworthy, and cannot simply be dismissed outright. In Gupta's study, even though this study was powered to find a meaningful difference in outcomes, they were only able to do so in bivariate analyses. After controlling for important confounders (such as severity of respiratory failure and presenting illness), significance was lost, although a trend towards earlier extubation remained ($p = 0.07$).

Although we were able to demonstrate that DSI in our meta-analysis only produced a slightly higher rate of adverse events, it is important to note that the studies included only assessed short-term events. Further studies may be warranted to rule out that long-term psychological complications do not occur with the more awake state in a stressful, potentially painful situation, such as suggested increased rates of post-traumatic stress disorder in DSI in adults [21].

The highly significant reduction in total midazolam dosages in the DSI group versus the PS group was derived from two studies. Midazolam is the most commonly used drug for sedation in critically ill children, often combined with an opioid such as morphine for analgesia [22]. Despite its popularity, attempts to minimize total doses are important as oversedation leads to tolerance and withdrawal symptoms, in addition to delayed recovery and difficult withdrawal [23]. The demonstrated reduction in total doses in our meta-analysis should therefore be beneficial in the PICU setting, if undersedation has not led to any adverse events. Additionally, benzodiazepines have been implicated in observational studies as contributing factors to PTSD in adults [24]. Again, that cannot be generalized to children.

It is difficult to compare our results with adult data as there are many confounding factors. One is the use of other medications in adults such as propofol, which is contraindicated in many situations in the PICU [22]. Renal excretion may vary with age, as may drug metabolism, both of which affect elimination half-life. Assessment of wakefulness is also a challenge in children, as opposed to simple ability to follow instructions in adults. Despite the presence of validated scales such as COMFORT [25], another common confounding factor in adult studies if previous drug and alcohol consumption [4] but fortunately that is not a challenge in most critically ill children.

In our systematic review, we believe we included all applicable articles without bias. We limited our review to three trials with similar methods, excluding Curley et al.'s data [16] because they compared protocolized sedation to usual care in an effort to avoid this form of heterogeneity.

As for the actual trials included, there was a low risk of attrition or other forms of bias. Although it was not feasible to blind any of the parties in these randomized controlled trials, future research may hopefully find strategies to blind outcome assessors. Clinician decision-making can influence weaning strategies, which will ideally be standardized, and outcomes independently assessed by a blinded clinician or researcher. Conceptual heterogeneity may occur with systematic reviews, where there are significant differences in study designs and outcomes.

We have several limitations in our study. One was the small number of randomized control trials involving DSI in children. However, motivated by the importance of this topic and potential for benefit in the PICU setting, we decided to proceed after finding other systematic reviews with small numbers and were able to get approval for the study through Prospera. Over approximately 15 months since then, there have been no recent publications of RCTs comparing DSI to protocolized sedation in children. Other limitations include the observation that the articles did their best to have balanced arms, but details as to severity of illness, neurologic illness, immunocompetence, and weaning procedure were not detailed. Additionally, the trials focused on midazolam as the initial agent, despite the fact that analgesia first is a more common approach according to the ICU Liberation Campaign [26]. Imprecision is also a concern in this meta-analysis, especially with the data for duration of mechanical ventilation, as seen with excessively wide CIs around the pooled data.

5. Conclusion

DSI was found to be superior to routine sedation in three of the four outcomes that were our focus in this systematic review and meta-analysis. There were shorter lengths of PICU stay and duration of mechanical ventilation, as well as reduced total doses of midazolam. However, there was also a higher rate of adverse events. Future research should focus on larger sample sizes, elimination of confounding factors, studying long-term effects of DSI on patients, and effect on nursing and respiratory therapist workload.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

No funding was received.

ORCID

Mona A. Azzam http://orcid.org/0000-0002-3308-4015
Mohammad H. Hussein http://orcid.org/0000-0001-8278-7094
Ghada A. Kamhawy http://orcid.org/0000-0002-9003-978X

Authors' contributions

MA: Idea, discussions with team for methodology, writing of discussion, review of results, preparation of manuscript.

EE: Analysis of studies and data extraction, writing of results, review of manuscript.

ST: Analysis of studies and data extraction, writing of results, review of manuscript.

AS: Discussions with team for methodology, review of results, review of manuscript.

MH: Data extraction, review of results, review of manuscript.

KS: Statistics, review of results, review of manuscript.

GK: Idea, PROSPERA submission, writing of methodology, participation in analysis of studies and data extraction, review of results, and participation in preparation of manuscript.

References

[1] Girard TD, Shintani AK, Jackson JC, et al. Risk factors for post-traumatic stress disorder symptoms following critical illness requiring mechanical ventilation: a prospective cohort study. Crit Care. 2007;11(1):R28.
[2] Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013;41(1):263–306.
[3] Shinotsuka CR, Salluh JI. Perceptions and practices regarding delirium, sedation and analgesia in critically ill patients: a narrative review. Rev Bras Ter Intensiva. 2013;25(2):155–161.
[4] Burry L, Rose L, McCullagh IJ, et al. Daily sedation interruption versus no daily sedation interruption for critically ill adult patients requiring invasive mechanical ventilation. Cochrane Database Syst Rev. 2014;7:CD009176.
[5] Mehta S, Burry L, Martinez-Motta JC, et al. A randomized trial of daily awakening in critically ill patients managed with a sedation protocol: a pilot trial. Crit Care Med. 2008;36(7):2092–2099.
[6] Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (awakening and breathing controlled trial): a randomised controlled trial. Lancet. 2008;371(9607):126–134.
[7] Mehta S, Burry L, Cook D, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. Jama. 2012;308(19):1985–1992.
[8] Augustes R, Ho KM. Meta-analysis of randomised controlled trials on daily sedation interruption for critically ill adult patients. Anaesth Intensive Care. 2011;39(3):401–409.
[9] O'Connor M, Bucknall T, Manias E. A critical review of daily sedation interruption in the intensive care unit. J Clin Nurs. 2009;18(9):1239–1249.
[10] Gupta K, Gupta VK, Jayashree M, et al. Randomized controlled trial of interrupted versus continuous sedative infusions in ventilated children. Pediatr Crit Care Med. 2012;13(2):131–135.
[11] Vet NJ, de Wildt SN, Verlaat CW, et al. A randomized controlled trial of daily sedation interruption in critically ill children. Intensive Care Med. 2016;42(2):233–244.
[12] Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g7647.
[13] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
[14] Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135.
[15] Verlaat CW, Heesen GP, Vet NJ, et al. Randomized controlled trial of daily interruption of sedatives in critically ill children. Paediatr Anaesth. 2014;24(2):151–156.
[16] Curley MA, Wypij D, Watson RS, et al. Protocolized sedation vs usual care in pediatric patients mechanically ventilated for acute respiratory failure: a randomized clinical trial. JAMA. 2015;313(4):379–389.
[17] De Cristofano A, Peuchot V, Canepari A, et al. Implementation of a ventilator-associated pneumonia prevention bundle in a single PICU. Pediatr Crit Care Med. 2016;17(5):451–456.
[18] Nassar AP, Zampieri FG, Ranzani OT, et al. Protocolized sedation effect on post-ICU posttraumatic stress disorder prevalence: A systematic review and network meta-analysis. J Crit Care. 2015;30(6):1278–1282.
[19] Wickstrom G, The BT. "Hawthorne effect"–what did the original Hawthorne studies actually show? Scand J Work Environ Health. 2000;26(4):363–367.
[20] Nassar AP, Park M. Sedation protocols versus daily sedation interruption: a systematic review and meta-analysis. Rev Bras Ter Intensiva. 2016;28(4):444–451.
[21] Parker AM, Sricharoenchai T, Raparla S, et al. Posttraumatic stress disorder in critical illness survivors: a metaanalysis. Crit Care Med. 2015;43(5):1121–1129.

[22] Playfor S, Jenkins I, Boyles C, et al. Consensus guidelines on sedation and analgesia in critically ill children. Intensive Care Med. 2006;32(8):1125–1136.
[23] Ista E, de Hoog M, Tibboel D, et al. Implementation of standard sedation management in paediatric intensive care: effective and feasible? J Clin Nurs. 2009;18 (17):2511–2520.
[24] Wade DM, Howell DC, Weinman JA, et al. Investigating risk factors for psychological morbidity three months after intensive care: a prospective cohort study. Crit Care. 2012;16(5):R192.
[25] van Dijk M, Peters JW, van Deventer P, et al. The COMFORT behavior scale: a tool for assessing pain and sedation in infants. Am J Nurs. 2005;105 (1):33–36.
[26] Zimmerman JJ, Watson RS, Ely EW. Daily sedation interruption in children warrants further study. Intensive Care Med. 2016;42(6):1101–1102.