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Review article

The impact of analgosedation on mortality and delirium in critically ill patients: A systematic review and meta-analysis ☆

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ABSTRACT

Objectives: To assess the impact of analgosedation on mortality and delirium in critically ill patients.
Research methodology: A systematic review and meta-analysis was conducted to identify studies through Pubmed, Cochrane Library, Embase and Web of Science published from June 2017 to July 2018. Only articles published in English were considered. The Cochrane Collaboration Risk of Bias Tool was used to evaluate the methodological quality of randomised trials, while Newcastle-Ottawa Scale (NOS) was used for cohort studies.
Results: Seventeen eligible studies were identified, including 2298 patients (1170 in the experimental group and 1128 in the control group). Varying analgesics and sedatives were investigated, showing a high clinical heterogeneity. Analgosedation significantly decreased the ICU mortality rate when compared to conventional analgesia and sedation [odds ratio (OR) 0.72, 95%CI 0.53–0.97; P = 0.03]. No significant difference was demonstrated in 28-day/hospital mortality rate [OR 0.91, 95%CI 0.70–1.18; P = 0.48] or in the incidence of delirium [OR 1.06, 95%CI 0.78–1.45; P = 0.70]. However, subgroup analysis of trials indicated a significant increase in the delirium rate (OR: 1.88, 95%CI 1.14–3.10, p = 0.01).
Conclusion: The ICU mortality was decreased by implementing analgosedation, but the hospital mortality and the delirium rates were not. Because of the absence of higher quality study designs, clinical heterogeneity and inclusion of small number of studies, the analysis results must be cautiously interpreted.

Implications for clinical practice

- Some short-term outcomes could be improved by implementing analogsedation. Only the multi-component interventions confer the overall clinical endpoints benefits.
- Delirium is associated with analogsedation in high quality studies, especially in morphine administration. The true cause-effect relationship should be fully elucidated further.
- Future investigations on the pathophysiology between analgosedation and mortality and the use of adjunctive opioid-sparing agents are warranted.

Introduction

Analgesic and sedative medications are widely used in patients to achieve patient comfort and tolerance in the intensive care unit (ICU). Hypnotic-based sedation, where midazolam or propofol is used, with opioids or another analgesic added as needed, has been a common conventional regimen (Park et al., 2007). Sedation with

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these hypnotic components means that the patients do not complain of pain, but their discomfort and pain are difficult to assess in an unconscious state (Tonner et al., 2003). This is nothing but the reversal from sedation-analgesia to analgesia-based sedation and this has been introduced with the primary goal of addressing pain and discomfort and then if necessary, adding sedation (Sessler and Varney, 2008; Egerod, 2009). According to the pooled analysis, protocol-based (analgesia/analgosedation) pain and sedation assessment and management programs reduce sedative requirements, duration of mechanical ventilation, ICU length of stay (LOS), and pain intensity when compared with usual therapy (Devlin et al., 2018).

Delirium is a clinical syndrome caused by substance intoxication or withdraw, or medication side effects, which is characterised by perceptual disturbances, inattention, alteration of consciousness with reduced ability to focus, sustain or shift attention (American Psychiatric Association, 2013). High rates of delirium have been demonstrated in patients in ICUs (70%) (McNicoll et al., 2003). Patients with delirium experience prolonged hospitalisation, functional and cognitive decline and higher mortality (Fong et al., 2012; Steinmetz et al., 2013). Some common factors such as drugs, toxins (e.g., opioids, sedatives), infection and immobility might precipitate in the cause of delirium (Barr et al., 2013). Analgosedation that spares opioid and sedative use has potential advantages in preventing delirium.

Analgosedation, which is also known as analgesia-first sedation or analgesia-based sedation, is explored in this article with the hope to provide better pain management and sedation to critically ill patients. As the benefits of this approach have not been observed across mortality and delirium (Devlin et al., 2018), we aimed to perform a systematic review and meta-analysis to evaluate these questions.

Methods

The PRISMA statement (Moher et al., 2009) is a 27-item checklist that was used for reporting the items for this systematic review and meta-analysis. The study protocol was developed prior to the initiation of the search strategy and has been registered with PROSPERO.

Search strategy

Four electronic databases (Pubmed, Embase, Cochrane Library, Web of Science databases) were searched. There were no date limits imposed on the database searches. Searches were conducted between June–December 2017 and updated in July 2018. The search was developed based on PICO (Higgins and Green, 2011) method, wherein the population presented was ICU adult patients, exposed to analogsedation, conventional analgesia and sedation was used as control and the outcomes are mortality (including ICU and hospital) and delirium.

The search strategy included the following key words: ‘‘analogsedation”, ‘‘analog-sedation”, ‘‘analgesia-based sedation”, ‘‘no sedation”. Reference lists of articles retrieved (reviews also) were also manually explored to identify potentially eligible studies.

Study selection and inclusion criteria

All citations were exported into EndNote. Duplicates were removed and CTW and YM assessed the titles and abstracts against the eligibility criteria (shown in Table 1). Only studies published in English language were considered for inclusion. Full papers were obtained for studies that are deemed to be ‘included’ or ‘uncertain’ and again, these papers were screened against the inclusion criteria. Any disagreements were resolved by reaching a consensus.

Table 1
Meta-analysis inclusion and exclusion criteria.

	Inclusion criteria	Exclusion criteria
Language	English	Non-English
Publication dates	All years	/
Participants	– Ages ≥ 18 years old – Treated with mechanical ventilation	– Ages ≤18 years old – Pregnant – Had no cerebral contact
Setting	– Intensive care unit	– Other unit
Intervention	– Analgesia-based sedation – Analogsedation – No sedation	– Not accord with the inclusion criteria
Study design	– Randomised controlled trial – Case control study – Cohort study	– Case report – Review – Protocol – Commentary – Letter
Outcome	– ICU/14-day mortality – Hospital/28-day mortality – The incidence of delirium	– data about mortality or delirium had not to be available

Data extraction

A customised extraction form was used to collect the following data: author, publication year, study design, interventions used in the treatment and control groups, sample size of the two groups and outcomes in the meta-analysis. Authors were not contacted for additional information.

Quality assessment

The study quality of randomised trials were assessed independently by two reviewers (CTW and YM) using the Cochrane Collaboration Risk of Bias Tool (Higgins and Green, 2011). The quality of cohort studies was evaluated by Newcastle-Ottawa Scale (NOS) (Wells et al., 2014). Studies with NOS score ≥5 with the inclusion of appropriate statistical analysis were considered to be high methodological quality. Any disagreements were resolved by reaching consensus.

Statistical analysis

Review Manager 5.3 and Stata 14.0 were used for meta-analysis and Egger’s regression test. For dichotomous variable, the Mantel-Haenszel (MH) model was used to obtain Odds Ratio (OR) and 95% CI. Heterogeneity between studies was assessed by I^2 statistic. I^2 values of 25, 50, and 75% were considered to be low, moderate, and high degrees of heterogeneity, respectively (Higgins et al., 2003). A subgroup analysis for meta-analysis (different study designs such as randomised controlled trials, prospective cohort studies and retrospective studies) (Higgins and Green, 2011) was conducted to lessen the heterogeneity. $P < 0.05$ was considered to be statistically significant. Egger’s regression model was used to detect publication bias when the number of analysed studies was enough (Egger et al., 1997).

Results

A summary of study selection process was presented in Fig. 1. The literature search yielded 2173 citations. Of these, 2042 studies

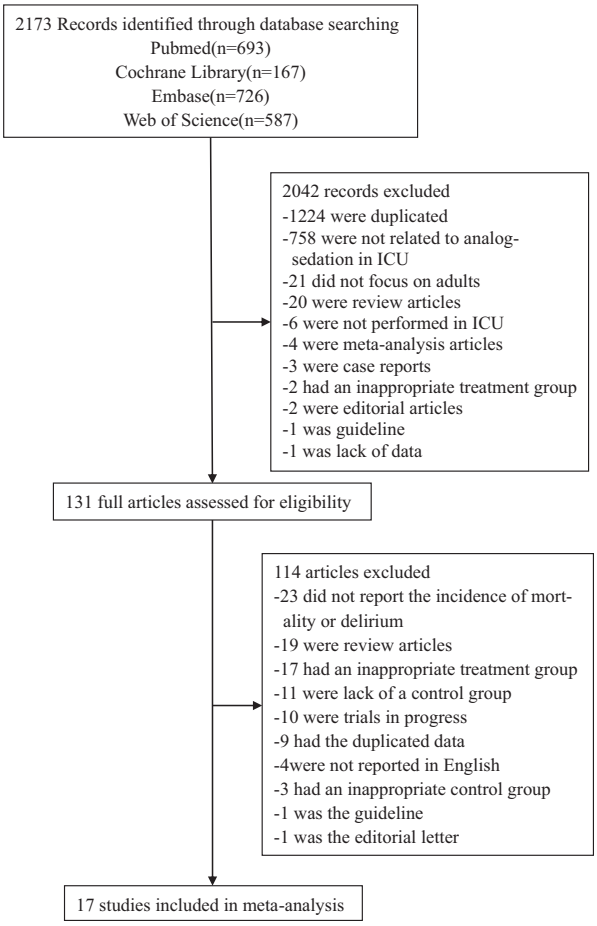

Fig. 1. PRISMA flowchart.

were removed because of duplication and other reasons. Full-text versions of 131 papers were examined and 114 papers were deemed to be ineligible. Finally, a total of 17 studies were considered eligible for analysis.

Study characteristics

The key characteristics of the included studies were presented in Table 2. Seven studies were conducted at multiple sites in Europe (Karabinis et al., 2004; Breen et al., 2005; Muellejans et al., 2006; Park et al., 2007; Egerod et al., 2010; Strøm et al., 2010; Schneider et al., 2017), five in America (Robinson et al., 2008; Tedders et al., 2014; Faust et al., 2016; Robisheaux et al., 2017; Shurtleff et al., 2018), two in South America (Bugedo et al., 2013; Nassar et al., 2014), two in Asia (Ikeda-Maquiling, 2014; Xing et al., 2015) and one in Africa (Bassuoni et al., 2012). These 17 articles included a total of 2298 patients, where 1170 were in the treatment group and 1128 in the control group.

The definition of analgosedation was described above. However, the strategy of conventional analgesia and sedation was categorised into two themes: (1) Standard hypnotic-based sedation stated before and (2) the routine clinical practice at each investigating site, wherein the infusion rates of analgesic and sedation were not specified (Robinson et al., 2008; Egerod et al., 2010; Bugedo et al., 2013).

Twelve studies compared an opioid (fentanyl, morphine, or remifentanil) with propofol or midazolam (Karabinis et al., 2004; Breen et al., 2005; Muellejans et al., 2006; Park et al., 2007; Robinson et al., 2008; Egerod et al., 2010; Strøm et al., 2010; Bassuoni et al., 2012; Bugedo et al., 2013; Nassar et al., 2014; Tedders et al., 2014; Faust et al., 2016). Two studies did not report specific data (Ikeda-Maquiling, 2014; Xing et al., 2015) and the remaining three studies compared sufentanil, ketamine or multiple analgesics with a hypnotic (benzodiazepine, propofol or dexmedetomidine) (Schneider et al., 2017; Robisheaux et al., 2017; Shurtleff et al., 2018). The recommended medication dosing varied greatly from one study to another.

With regards to the outcomes, nine studies focused on ICU mortality (Karabinis et al., 2004; Breen et al., 2005; Park et al., 2007; Egerod et al., 2010; Strøm et al., 2010; Bassuoni et al., 2012; Tedders et al., 2014; Xing et al., 2015; Schneider et al., 2017), nine on hospital mortality (Park et al., 2007; Robinson et al., 2008; Strøm et al., 2010; Bugedo et al., 2013; Ikeda-Maquiling, 2014; Nassar et al., 2014; Xing et al., 2015; Faust et al., 2016; Shurtleff et al., 2018) and eight were on delirium rate (Muellejans et al., 2006; Robinson et al., 2008; Strøm et al., 2010; Bassuoni et al., 2012; Nassar et al., 2014; Tedders et al., 2014; Robisheaux et al., 2017; Shurtleff et al., 2018). Studies that reported 28-day mortality (Robinson et al., 2008; Bugedo et al., 2013) were pooled with those studies reporting hospital mortality.

Quality assessment

The results of randomised studies based on the Cochrane Collaboration Risk of Bias Tool and the cohort studies and case control studies based on the NOS were presented in Supplementary File 1 and 2, indicating a medium to high standard data was collected.

Synthesis of results

ICU mortality (Fig. 2)

A statistically significant decrease was found in ICU mortality in analgesia-based sedation group when compared to sedative-hypnotic therapy (overall OR: 0.72, 95%CI 0.53–0.97, P= 0.03). Also no heterogeneity was observed (I^2 = 0%). However, for subgroup analysis of trials, no significant difference was found (OR:0.64, 95%CI 0.39–1.04, P = 0.07; I^2 = 0%) (Karabinis et al., 2004; Breen et al., 2005; Strøm et al., 2010; Bassuoni et al., 2012; Nassar et al., 2014). Similar results were obtained for subgroup analysis of cohort studies (OR: 0.80, 95%CI 0.54–1.18, P = 0.26; I^2 = 10%) (Park et al., 2007; Egerod et al., 2010; Schneider et al., 2017).

Hospital mortality (Fig. 3)

There were no significant differences observed in hospital mortality between the two therapy groups (overall OR: 0.91, 95%CI 0.70–1.18, P = 0.48), and showed a moderate heterogeneity (I^2 = 32%). Similar results were obtained for the subgroup analysis of trials (OR: 0.62, 95%CI 0.34–1.15, P = 0.13; I^2 = 0%) (Strøm et al., 2010; Nassar et al., 2014) and cohort studies (OR: 1.07, 95%CI 0.74–1.55, P = 0.72; I^2 = 0%) (Park et al., 2007; Bugedo et al., 2013; Ikeda-Maquiling, 2014).

Delirium (Fig. 4)

No significant differences were observed in the delirium rate between the two therapies (overall OR: 1.06, 95%CI 0.78–1.45, P = 0.70), and showed a high heterogeneity (I^2 = 67%). Similarly, a high heterogeneity (I^2 = 66%) was observed in the subgroup analysis of case control studies (OR: 0.72, 95%CI 0.48–1.08, P = 0.12) (Robinson et al., 2008; Tedders et al., 2014; Robisheaux et al., 2017; Shurtleff et al., 2018). For the subgroup analysis of trials, the delirium rate was increased significantly in the analogsedation group (OR: 1.88, 95%CI 1.14–3.10, P = 0.01), showing a moderate heterogeneity (I^2 = 38%) (Muellejans et al., 2006; Strøm et al., 2010; Bassuoni et al., 2012; Nassar et al., 2014).

Table 2
Descriptive Characteristics of the included Studies.

Authors (publication year)	Study Design	Continent	Intervention (sample size)	Control (sample size)	Outcomes
Karabinis et al. (2004)	RCT	Europe	**Analgesia-based sedation (n = 84):** **Analgesia:** Remifentanil 9–60 μg/kg/h **Sedation if required:** Propofol 0.5–4 mg/kg/h (first 3 days) or midazolam 0.03–0.3 mg/kg/h (days 3–5)	**Hypnotic-based sedation(n = 77):** **Sedation:** Propofol (first 3 days) or midazolam (days 3–5) **Analgesia if required:** Fentanyl 0.1–7.9 μg/kg/h (n = 37) or morphine 0–6.8 mg/kg/h (n = 40)	ICU mortality
Breen et al. (2005)	RCT	Europe	**Analgesia-based sedation (n = 57):** **Analgesia:** Remifentanil 6–45 μg/kg/h **Sedation if required:** Midazolam 2 mg boluses	**Hypnotic-based sedation(n = 48):** **Sedation:** Midazolam **Analgesia if required:** Morphine or fentanyl	ICU mortality
Muellejans et al.(2006)	RCT	Germany	**Analgesia-based sedation(n = 40):** **Analgesia:** Remifentanil 6–60 μg/kg/h **Sedation if required:** Propofol 0.5–4 mg/kg/h	**Hypnotic-based sedation (n = 39):** **Sedation:** Midazolam 0.03–0.2 mg/kg bolus, then 0.02–0.4 mg/kg/h **Analgesia if required:** fentanyl 1–2 μg/kg boluses, then 1–7 μg/kg/h	Delirium
Park et al. (2007)	Prospective pre-/post-intervention study	UK	**Analgesia-based sedation (n = 95):** **Analgesia:** Remifentanil 6–15 μg/kg/h **Sedation if required:** Propofol 0.5–5 mg/kg/h and Midazolam 1 mg bolus	**Hypnotic-based sedation (n = 111):** **Sedation:** Increments of midazolam (2.5 mg) **Analgesia if required:** morphine (2.5 mg), add in morphine and propofol by infusion	ICU mortality Hospital mortality
Robinson et al.(2008)	Retrospective pre-/post study	America	**Analgesia–Delirium–Sedation Protocol (n = 68):** **Analgesia:** Fentanyl: 50-100mcg, 50-100mcg/h **Sedation if required:** Propofol 5-80 mcg/kg/min	**Non-protocolized (n = 75):** Sedated as usual	Hospital mortality
Strøm et al. (2010)	RCT	Denmark	**No sedation strategy (n = 55):** **Analgesia:** Morphine 2.5 or 5 mg boluses **Sedation if required:** Propofol 20 mg/mL	**Sedation with daily interruption (n = 58):** **Sedation:** Propofol 0.7 mg/kg/h **Analgesia if required:** morphine 2.5 or 5 mg boluses	ICU mortality Delirium
Egerod et al. (2010)	Prospective pre-/post-intervention study	Denmark	**Analgosedation (n = 109):** **Analgesia:** Remifentanil infusion up to 45 μg/kg/h or increase dose of fentanyl infusion **Sedation if required:** Propofol or midazolam	**Non-protocolized(n = 106):** Sedated as usual	ICU mortality
Bassuoni et al. (2012)	RCT	Egypt	**No sedation strategy (n = 115):** **Analgesia**: Morphine 2.5–5 mg boluses **Sedation if required:** Propofol	**Sedation with daily interruption (n = 115):** **Sedation:** Midazolam **Analgesia if required:** Morphine	ICU mortality Delirium
Bugedo et al. (2013)	Prospective pre-/post-intervention study	Chile	**Analgesia-based sedation(n = 132):** **Analgesia**: Fentanyl 0.6–3.6 μg/kg/h **Sedation if required:** Midazolam 0.015–0.09 mg/kg/h	**Non-protocolised (n = 155):** Sedated as usual	Hospital mortality
Ikeda-Maquiling (2014)[a]	Prospective cohort study	Philippines	**No sedation strategy (n = 38)**	**A strategy with early sedation (n = 18)**	Hospital mortality
Nassar et al. (2014)	RCT	Brazil	**Intermittent sedation strategy (n = 50):** **Analgesia**: Fentany1 50–150 μg boluses or continuous infusion **Sedation if required:** Propofol	**Sedation with daily interruption (n = 50):** **Sedation:** Midazolam or propofol **Analgesia if required:** Fentanyl	ICU mortality Delirium
Tedders et al. (2014)	Retrospective study	America	**Analgesia-based sedation (n = 30):** **Analgesia**: Fentanyl	**Traditional sedation regimen (n = 30):** **Sedation:** Midazolam **Analgesia if required:** Fentanyl	Delirium
Xing et al. (2015)	Retrospective cohort	China	**No sedation strategy (n = 63)**	**Sedation strategy (n = 28)**	ICU mortality Hospital mortality
Faust et al. (2016)	Retrospective pre-/post study	America	**Analgosedation (n = 79):** **Analgesia**: Fentanyl or narcotic analgesics boluses or continuous infusion **Sedation if required:** Propofol or dexmedetomidine	**Conventional analgesia and sedation (n = 65):** **Sedation**: propofol or midazolam **Analgesia if required**: Morphine	Hospital mortality
Robisheaux et al. (2017)	Retrospective study	Amrica	**Analgesia-based sedation (n = 65):** **Analgesia**: Solely used analgesics (Fentanyl, Morphine, Hydromorphone or Ketamine)	**Conventional analgesia and sedation (n = 77):** **Sedation:** Benzodiazepines	Delirium
Schneider et al. (2017)	Prospective pre-/post-intervention study	Germany	**Benzodiazepine-free strategy (n = 50):** **Analgesia**: sufentanil, nonsteroidal anti-inflammatory drugs	**Conventional analgesia and sedation (n = 36):** **Sedation:** Benzodiazepine and propofol	ICU mortality
Shurtleff et al. (2018)	Retrospective study	America	**Ketamine based strategy (n = 39):** **Analgesia**: Ketamine	**Conventional analgesia and sedation (n = 40):** **Sedation:** Propofol or dexmedetomidine	Hospital mortality Delirium

[a] Abstract only available. RCT: randomised controlled trial; ICU, intensive care unit.

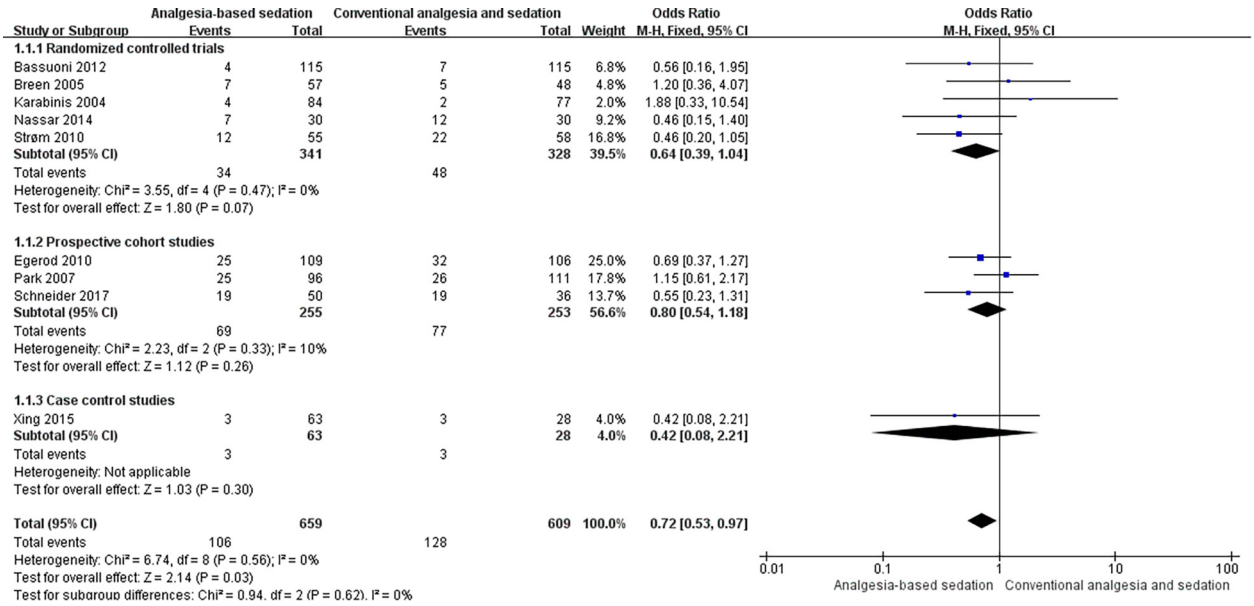

Fig. 2. Meta-analysis of the association betweem analogsedation and ICU mortality.

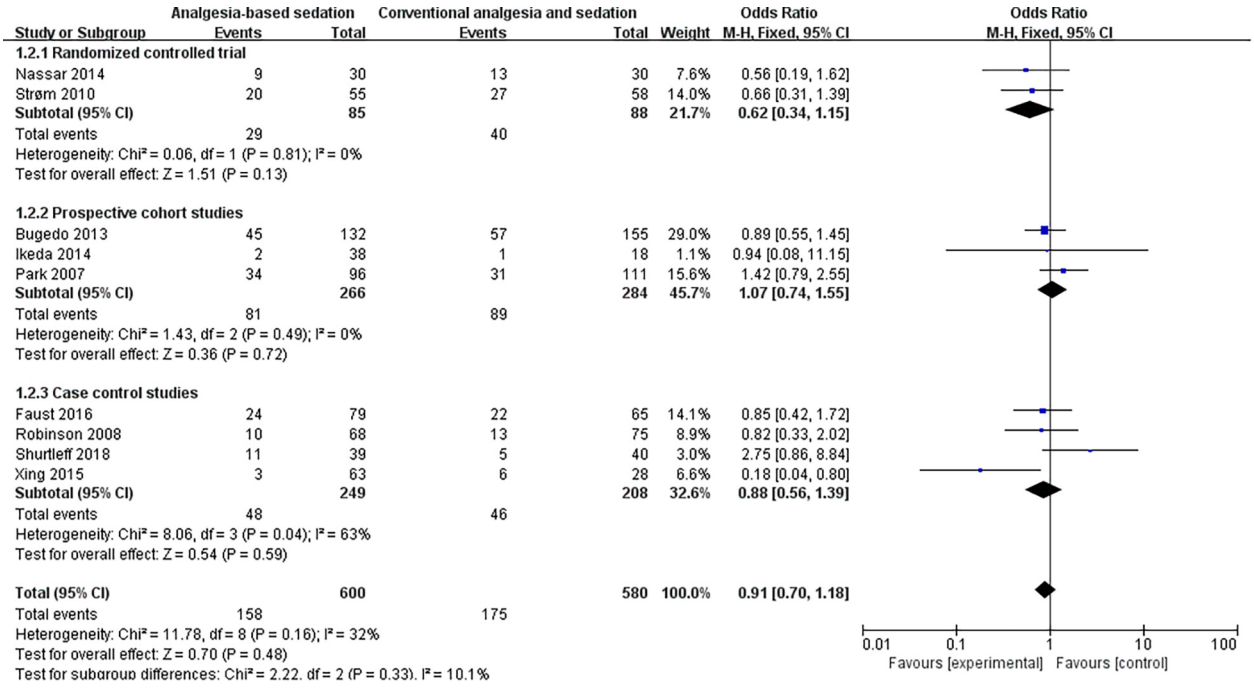

Fig. 3. Meta-analysis of the association between analogsedation and 24-d/hospital Mortality.

Discussion

This systematic review aimed to locate and produce the highest quality evidence available to determine the correlation between analogsedation and adverse effects such as mortality rate and delirium in critically ill patients. These findings demonstrated that the ICU mortality was lowered when analogsedation was implemented. However, the approach did not confer the 28-day/hospital mortality and the delirium rate benefits.

Analogsedation was defined as either analgesia-first sedation (i.e., an analgesic, usually an opioid, used before a sedative to reach the sedative goal) or analgesia-based sedation (i.e., an analgesic, usually an opioid, used instead of a sedative to reach the sedative goal) (Devlin et al., 2018). The primary focus of this regimen was to make treatment pain a priority in providing sedatives, aiming to achieve and maintain a mild level of sedation. Interestingly, findings about analogsedation in this review were in accordance with the guideline recommendations, suggesting that the targeting light levels of sedation or minimising benzodiazepines to improve short-term outcomes, but not the long-term ones (Devlin et al., 2018). Promising studies have demonstrated that the therapy minimised the accumulation of sedative effects, shortened ventilator time and ICU length of stay (Karabinis et al., 2004; Breen et al., 2005). Similarly, a hypothesis could be formulated for the advantages of analogsedation discussed above, which remains beneficial in decreasing the short-term mortality (Shehabi et al., 2013).

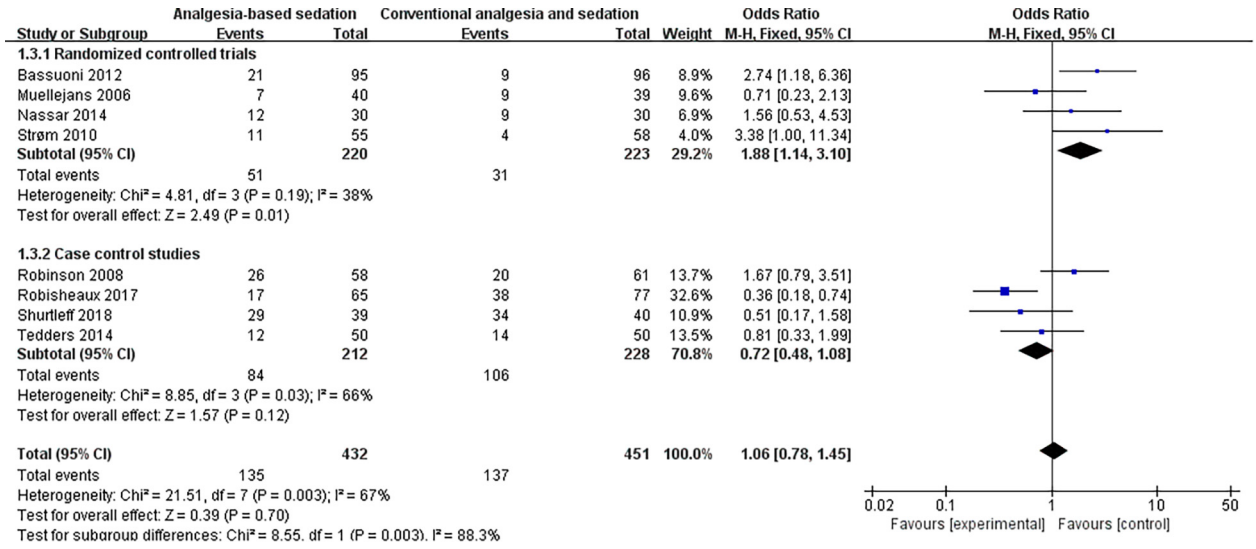

Fig. 4. Meta-analysis of the association between analogsedation and delirium.

However, the short-term outcomes differed from the post-ICU discharge measurements. Light sedation showed no association with reduced long-term mortality, delirium prevalence or post-traumatic stress disorder incidence (Strøm et al., 2010; Shehabi et al., 2012). It has been reported that hospital mortality in critically ill patients was independently related not only to sedation, but also infection, antibiotic choice, renal replacement therapy need, mechanical ventilation status and many other factors (Jarrell et al., 2018). What's more, the use of analgosedation in the management of ICU sedation resulted in a high incidence rate of recall for unpleasant events, hallucinations and nightmares (Rundshagen et al., 2002). In addition, opioids were associated with immunosuppression (Nseir et al., 2009) and these adverse effects could be devastating in critically ill patients and bad for long-term survival.

An assumption that only multi-component interventions including strategies to improve wakefulness, and to reduce immobility could improve the long-term outcomes (Moon et al., 2015; Devlin et al., 2018). In the meantime, continuous clarification of the pathophysiology between analgosedation and mortality was strongly recommended.

Nearly 70 percent of critically ill adults had experienced delirium in ICU (McNicoll et al., 2003). Factors that increased the risk of delirium were classified into those that increased baseline vulnerability and those that precipitated in the disturbance (Elie et al., 1998). The former included advanced age and sensory impairment and the latter included drugs, infections, brain disorders, physical disorders malnutrition and so on. Studies have found that the protracted delirium was associated with increased one-year mortality when compared with those whose symptoms has been resolved more quickly (Kiely et al., 2009). Although delirium was considered to be potentially reversible, impairments might be prolonged and perhaps be permanent (Shehabi et al., 2010). It has been found that patients with delirium are more likely to have long-term cognitive problems than those who did not suffer from the syndrome (van den Boogaard et al., 2012). So, deliriogenic patients should be cautiously evaluated as the syndrome is associated with a poor quality of life.

The overall meta-analysis here showed no significant difference in the incidence of delirium between the strategies. For subgroup analysis of trials, however, the delirium rate was increased significantly in the analogsedation group. The heterogeneity of several factors might explain the variable outcomes observed in delirium rate.

Firstly, although delirium is more commonly associated with benzodiazepines, it has also been associated with the use of opioid analgesics (Agarwal et al., 2010). Findings from two trials showed that the incidence of delirium was higher in the morphine-only group (Strøm et al., 2010; Bassuoni et al., 2012). There were data showing that morphine possessed deleriogenic effects due to drug accumulation and its comparatively longer duration of action (Dubois et al., 2001). So, carefully analgesic dosing titration is important in balancing the benefits versus risks of opioid exposure (Georgiou et al., 2015; Puntillo and Naidu, 2016).

Secondly, sedation and pain rating scales were not standardised across the studies, making it difficult to correlate the multitude of scales that are commonly used in clinical practice, with the aggregate results of the included studies. Also, the studies differed in their exclusion criteria. While some reported patients with brain diseases who had a higher susceptibility to delirium would be excluded, while others did not. Moreover, the differences in choice of medication and dosing among the studies caused bias in the results. These variations in assessment scales, and materials and methods caused complications in the meta-analysis results.

Thirdly, delirium is a multi-factorial disorder. An early study showed that analgesics and sedatives accounted for only 30 percent of all cases (Francis, 1996). So, not single but interventions that managed many of the modifiable risk factors would have an important effect on delirium reduction (Clegg et al., 2014).

Despite the recommendations of analgosedation in the guideline (Devlin et al., 2018), clinicians must be cognizant that some patients might still require a deeper level of sedation for optimal management. It is therefore regarded as a patient-centred approach, derived by the bedside clinician, which was best and should be used to determine the appropriate goal for a deep sedation.

Limitations and strengths

The objectives of this review article included examination of clinical evidence regarding the safety of analgosedation and evaluate the role of the approach in the management of critically ill patients more carefully. It included thorough systematic reviews and large population size (of over 2000 patients in Asia, Europe and USA published over 14 years). However, there are some limitations.

Firstly, lack of standardised analgesia and sedation assessment measures, such as rating scales and target sedation goals, made it difficult to compare and utilise all the available information. Validated assessment tools for pain and agitation were recommended.

Secondly, lack of consideration for studying a variety of analgesics and sedatives should be acknowledged. The difficult questions included as to which agent would be the best choice for analgosedation and how to use them properly. Interestingly, both benzodiazepines and opioids were reported to predispose patients to develop delirium. Future investigations on the use of adjunctive opioid-sparing agents were warranted.

Thirdly, this review only considered studies reported in English language, which may have limited insights into the phenomenon of interest pertaining to non-English speaking groups. Moreover, the authors had not been contacted when the data were insufficient, which may result in the bias of the results. Additionally, all clinical trials, case control studies and cohort studies were included. However, selection of high quality studies with a uniform study design would result in more reliable results of the weighted data.

Conclusion

In summary, the results from this systematic review provided novel insights into the impact of analgesia-based sedation on mortality and delirium in critically ill patients. It was evident from the analysed results that the ICU mortality was decreased with the implementation of analogsedation, but the hospital mortality and the delirium rate were not. This implied that short-term outcomes could be improved by using this approach, but only the multicomponent interventions that could confer the benefits of long-term clinical endpoints. Interestingly, it identified delirium to be associated with analogsedation in high quality studies, especially in studies with morphine administration. However, the true cause-effect relationship has not been fully elucidated. It is therefore important that future well-designed investigations are warranted to clarify the safety of analgosedation in critically ill patients, including investigations with non-opioid agents.

PROSPERO registration number

CRD 42017068561.

Ethical statement

This manuscript is a systematic review and meta-analysis, so there is no ethical approval.

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Declaration of Competing Interest

There is no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.iccn.2019.06.004.

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