Cochrane Library

Cochrane Database of Systematic Reviews

Protocol-directed sedation versus non-protocol-directed sedation in mechanically ventilated intensive care adults and children (Review)

Aitken LM, Bucknall T, Kent B, Mitchell M, Burmeister E, Keogh SJ

Aitken LM, Bucknall T, Kent B, Mitchell M, Burmeister E, Keogh SJ.
Protocol-directed sedation versus non-protocol-directed sedation in mechanically ventilated intensive care adults and children.
Cochrane Database of Systematic Reviews 2018, Issue 11. Art. No.: CD009771.
DOI: 10.1002/14651858.CD009771.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Protocol-directed sedation versus non-protocol-directed sedation in mechanically ventilated intensive care adults and children

Leanne M Aitken[1,2,3], Tracey Bucknall[4,5], Bridie Kent[6,7], Marion Mitchell[3,8], Elizabeth Burmeister[2,9], Samantha J Keogh[10]

[1]School of Health Sciences, City, University of London, London, UK. [2]National Centre of Research Excellence in Nursing, Menzies Health Institute Queensland, Griffith University, Brisbane, Australia. [3]Intensive Care Unit, Princess Alexandra Hospital, Woolloongabba, Australia. [4]School of Nursing and Midwifery, Faculty of Health, Deakin University, Geelong, Australia. [5]Deakin University Centre for Quality and Patient Safety Research - Alfred Health Partnership, Alfred Health, Melbourne, Australia. [6]School of Nursing and Midwifery, Deakin University Centre for Quality and Patient Safety Research, Deakin University, Geelong, Australia. [7]School of Nursing and Midwifery, University of Plymouth, Plymouth, UK. [8]NHMRC Centre of Research Excellence in Nursing, Centre for Health Practice Innovation, Menzies Health Institute Queensland, Griffith University, Brisbane, Australia. [9]Nursing Practice and Development Unit, Princess Alexandra Hospital, Brisbane, Australia. [10]School of Nursing, Queensland University of Technology, Brisbane, Australia

Contact address: Leanne M Aitken, National Centre of Research Excellence in Nursing, Menzies Health Institute Queensland, Griffith University, Brisbane, Australia. leanne.aitken.1@city.ac.uk, l.aitken@griffith.edu.au.

Editorial group: Cochrane Emergency and Critical Care Group.
Publication status and date: Edited (no change to conclusions), published in Issue 12, 2018.

Citation: Aitken LM, Bucknall T, Kent B, Mitchell M, Burmeister E, Keogh SJ. Protocol-directed sedation versus non-protocol-directed sedation in mechanically ventilated intensive care adults and children. *Cochrane Database of Systematic Reviews* 2018, Issue 11. Art. No.: CD009771. DOI: 10.1002/14651858.CD009771.pub3.

ABSTRACT

Background

The sedation needs of critically ill patients have been recognized as a core component of critical care that is vital to assist recovery and ensure humane treatment. Evidence suggests that sedation requirements are not always optimally managed. Suboptimal sedation, both under- and over-sedation, have been linked to short-term (e.g. length of stay) and long-term (e.g. psychological recovery) outcomes. Strategies to improve sedation assessment and management have been proposed. This review was originally published in 2015 and updated in 2018.

Objectives

To assess the effects of protocol-directed sedation management compared to usual care on the duration of mechanical ventilation, intensive care unit (ICU) and hospital mortality and other patient outcomes in mechanically ventilated ICU adults and children.

Search methods

We used the standard search strategy of the Cochrane Anaesthesia, Critical and Emergency Care Group (ACE). We searched the Cochrane Central Register of Controlled trials (CENTRAL) (December 2017), MEDLINE (OvidSP) (2013 to December 2017), Embase (OvidSP) (2013 to December 2017), CINAHL (BIREME host) (2013 to December 2017), LILACS (2013 to December 2017), trial registries and reference lists of articles. (The original search was run in November 2013).

Selection criteria

We included randomized controlled trials (RCTs) and quasi-randomized controlled trials conducted in ICUs comparing management with and without protocol-directed sedation in intensive care adults and children.

Data collection and analysis

Two authors screened the titles and abstracts and then full-text reports identified from our electronic search. We assessed seven domains of potential risk of bias for the included studies. We examined clinical, methodological and statistical heterogeneity and used the random-effects model for meta-analysis where we considered it appropriate. We calculated the mean difference (MD) for duration of mechanical ventilation and risk ratio (RR) for mortality across studies, with 95% confidence intervals (CIs).

Main results

We included four studies with a total of 3323 participants (864 adults and 2459 paediatrics) in this update. Three studies were single-centre, patient-level RCTs and one study was a multicentre cluster-RCT. The settings were in metropolitan centres and included general, mixed medical-surgical, medical only and a range of paediatric units. All four included studies compared the use of protocol-directed sedation, specifically protocols delivered by nurses, with usual care. We rated the risk of selection bias due to random sequence generation low for two studies and unclear for two studies. The risk of bias was highly variable across the domains and studies, with the risk of selection and performance bias generally rated high and the risk of detection and attrition bias generally rated low.

When comparing protocol-directed sedation with usual care, there was no clear evidence of difference in duration of mechanical ventilation in hours for the entire duration of the first ICU stay for each patient (MD -28.15 hours, 95% CI -69.15 to 12.84; I^2 = 85%; 4 studies; adjusted sample 2210 participants; low-quality evidence). There was no clear evidence of difference in ICU mortality (RR 0.77, 95% CI 0.39 to 1.50; I^2 = 67%; 2 studies; 513 participants; low-quality evidence), or hospital mortality (RR 0.90, 95% CI 0.72 to 1.13; I^2 = 10%; 3 studies; adjusted sample 2088 participants; low-quality evidence). There was no clear evidence of difference in ICU length of stay (MD -1.70 days, 95% CI-3.71 to 0.31; I^2 = 82%; 4 studies; adjusted sample of 2123 participants; low-quality of evidence), however there was evidence of a significant reduction in hospital length of stay (MD -3.09 days, 95% CI -5.08 to -1.10; I^2 = 2%; 3 studies; adjusted sample of 1922 participants; moderate-quality evidence). There was no clear evidence of difference in the incidence of self-extubation (RR 0.88, 95% CI 0.55 to 1.42; I^2 = 0%; 2 studies; adjusted sample of 1687 participants; high-quality evidence), or incidence of tracheostomy (RR 0.67, 95% CI 0.35 to 1.30; I^2 = 66%; 3 studies; adjusted sample of 2008 participants; low-quality evidence). Only one study examined incidence of reintubation, therefore we could not pool data; there was no clear evidence of difference (RR 0.65, 95% CI 0.35 to 1.24; 1 study; 321 participants; low-quality evidence).

Authors' conclusions

There is currently limited evidence from RCTs evaluating the effectiveness of protocol-directed sedation on patient outcomes. The four included RCTs reported conflicting results and heterogeneity limited the interpretation of results for the primary outcomes of duration of mechanical ventilation and mortality. Further studies, taking into account differing contextual characteristics, are necessary to inform future practice. Methodological strategies to reduce the risk of bias need to be considered in future studies.

PLAIN LANGUAGE SUMMARY

Protocol-directed sedation to reduce duration of mechanical ventilation

Review question

We reviewed the evidence to determine if the use of protocol-directed sedation reduced the time on mechanical ventilation (method to mechanically assist breathing). We also determined if it reduced the intensive care unit (ICU) or hospital death rate in critically ill adults and children.

Background

Determining the sedation needs of critically ill people is an important part of critical care to help with recovery and guarantee humane treatment. Protocol-directed sedation is one management strategy that could be used as a way to reduce both under- and over-sedation. Protocol-directed sedation is sedation that is given by a nurse, pharmacist or other member of the healthcare team. That team member follows written, approved procedures outlined in a protocol (document). The initial order for protocol-directed sedation is written by a medical officer or physician. The aim of protocol-directed sedation is to improve patient outcomes, for example, to reduce the length of time a person is on mechanical ventilation or to reduce the death rate.

Search date

In this update we included evidence up to December 2017. This updates the previous version of the review which was current to November 2013.

Study characteristics

We searched scientific databases for studies that examined protocol-directed sedation in adult and paediatric intensive care patients. We identified four studies with 3308 participants (864 adults and 2459 paediatrics) to include in this review.

Key results

All of these included studies compared the use of protocol-directed sedation delivered by nurses to usual care (that is, non-protocol-directed sedation). There was no difference in the length of time mechanical ventilation was needed or in ICU or hospital deaths between people who received protocol-directed sedation and those people managed with usual care. There was a significant reduction in the number of days people treated with protocol-directed sedation spent in hospital, when compared to those managed with usual care. There was no difference between the two groups in the number of people who accidentally removed their breathing tube or required their tube to be reinserted after accidentally removing it.

In conclusion, the benefits of protocol-directed sedation delivered by nurses compared to usual care are currently unclear in relation to the important outcomes of length of time mechanical ventilation was needed or number of deaths.

Quality of the evidence

The evidence available to answer our review question is low to moderate. This is mainly due to the often conflicting results that were reported from the four eligible studies. Further studies need to be conducted to determine the effectiveness of this intervention.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Protocol-directed sedation management compared with usual care for sedation management in mechanically ventilated intensive care unit patients

Protocol-directed sedation management compared with usual care for sedation management in mechanically ventilated intensive care unit patients

Patient or population: mechanically ventilated ICU adults and children requiring sedation management

Settings: adult and paediatric intensive care units in USA, Australia and Iran

Intervention: protocol-directed sedation management

Comparison: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Usual care	Protocol-directed sedation management				
Duration of mechanical ventilation (measured in hours for the entire duration of the first ICU stay for each patient)	The mean duration of mechanical ventilation across control groups ranged from 93 to 228 hours	The mean duration of mechanical ventilation in the intervention groups was 28.15 hours shorter (95% CI -69.15 to 12.84)		3283 (4 studies) adjusted sample 2210	⊕⊕⊖⊖ **Low**[a, b]	There was inconsistency between the results of the included studies with Brook 1999 and Mansouri 2013 finding a significantly shorter duration of mechanical ventilation in the experimental group, while Bucknall 2008 and Curley 2015 found no difference, resulting in high heterogeneity. We assessed two included studies (Brook 1999; Mansouri 2013) as having a high risk of bias.
ICU mortality	**Medium-risk population**		RR 0.77 (95% CI 0.39 to 1.50)	513 (2 studies)	⊕⊕⊖⊖[a, b] **Low**	There was inconsistency between the results of the included studies with (Bucknall 2008), finding no difference in incidence of ICU mortality and Mansouri 2013 finding lower mortality in the experimental group, resulting in high heterogeneity. We assessed Mansouri 2013 as having a high risk of bias.
	216 per 1000	**166 per 1000** (84 to 324)				

Hospital mortality	**Medium-risk population** **140 per 1000**	**126 per 1000** (101 to 159)	RR 0.90 (95% CI 0.72 to 1.13)	3082 (3 studies) or adjusted sample n = 2008	⊕⊕⊖⊖[a, b] **Low**	All studies found no difference in hospital mortality, although Brook 1999 and Curley 2015 had a trend towards favouring the experimental group and Bucknall 2008 had a trend towards the control group, suggesting inconsistency in results, resulting in moderate heterogeneity. We assessed Brook 1999 as having a high risk of bias.
ICU length of stay (days)	The mean length of hospital stay across control groups ranged from 6.0 days to 14.0 days	The mean length of hospital stay in the intervention groups was 1.70 days shorter (95% CI -3.71 to 0.31)		3128 (4 studies) or adjusted sample n = 2123	⊕⊕⊖⊖ **Low**[a, b]	There was inconsistency between the results of the included studies with Brook 1999 and Mansouri 2013 finding a significantly shorter ICU length of stay in the experimental group while Bucknall 2008 and Curley 2015 found no difference, resulting in high heterogeneity. We assessed Brook 1999 and Mansouri 2013 as having a high risk of bias.
Hospital length of stay (days)	The mean length of hospital stay across control groups ranged from 19.2 days to 23.4 days	The mean length of hospital stay in the intervention groups was 3.09 days shorter (95% CI -5.08 to -1.10)		2927 (3 studies) or adjusted sample n = 1922	⊕⊕⊕⊖[b] **Moderate**	We assessed Brook 1999 as having a high risk of bias.
Adverse event - incidence of self-extubation (in ICU)	**Medium-risk population** **41 per 1000**	**36 per 1000** (23 to 59)	RR 0.88 (95% CI 0.55 to 1.42)	2761 (2 studies) or adjusted sample n = 1687	⊕⊕⊕⊕ **High**	
Adverse event - incidence of reintubation (in ICU)	**Medium-risk population** **132 per 1000**	**86 per 1000** (46 to 164)	RR 0.65 (95% CI 0.35 to 1.24)	321 (1 study)	⊕⊕⊖⊖ **Low**[b, c]	Only one study examined this outcome (Brook 1999), with no difference between the experimental group and the control group found. There was imprecision in results we assessed Brook 1999 as having high risk of bias.
Incidence of tracheostomy (in ICU)	**Medium-risk population** **63 per 1000**	**42 per 1000** (22 to 81)	RR 0.67 (95% CI 0.35 to 1.30)	3082 (3 studies) or adjusted	⊕⊕⊖⊖ **Low**[a, b]	There is inconsistency between the results of the three included studies with Brook 1999 and Curley 2015 finding a significantly lower rate of tracheostomy in the experimental group and Bucknall 2008 finding no difference, resulting in high heterogeneity. We assessed Brook 1999 as having a high risk of bias.

					sample n = 2008

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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).
CI: confidence interval; **ICU**: intensive care unit; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded one level due to heterogeneity of results between studies.
[b]Downgraded one level due to high risk of bias.
[c]Downgraded one level due to imprecision of results, likely due to small participant numbers.

BACKGROUND

Description of the condition

The sedation needs of critically ill patients are a core component of critical care. Intensive care patients are often treated with invasive and difficult-to-tolerate procedures and treatments. Ensuring comfort throughout this process assists recovery and ensures humane treatment (Mehta 2009). While appropriate sedation is essential for all patients, it is paramount for people receiving muscle relaxants. In association with sedation management, it is essential that adequate pain relief and anxiolysis be provided to all critically ill patients. There is growing evidence to suggest that sedation requirements are not optimally managed; one systematic review of 36 studies found a substantial incidence of suboptimal sedation, ranging from 1% to more than 50% of either sedation time or number of patients (Jackson 2009). More recent reports indicate that sedation practice has not improved in the past eight years, with up to half of all intensive care patients not being optimally sedated (Elliott 2013; Walsh 2016).

The detrimental impact of poor sedation practices is beginning to be understood and extends from under-sedation to over-sedation. Under-sedation has the potential to lead to agitated patients with compromized long-term psychological recovery, while over-sedation may lead to increased intensive care and hospital lengths of stay, poor long-term recovery (Mehta 2009), and increased mortality (Shehabi 2013). There is some evidence to suggest links between short-term measures (such as intensive care and hospital lengths of stay) (Jackson 2010; Kollef 1998; Schweickert 2008), adverse events (such as self-extubation) (Girard 2008), and longer-term aspects such as recall of time spent in the intensive care unit (ICU) and long-term psychological recovery (Jackson 2010; Ringdal 2006; Samuelson 2006).

Sedation refers to the administration of pharmacological agents designed primarily to induce a sedative effect in patients. It includes benzodiazepines, for example midazolam, lorazepam; sedative-hypnotic agents, for example propofol; and other specific sedative agents such as dexmedetomidine and clonidine. Sedation does not include pharmacological agents administered primarily for other reasons, such as analgesics, even though these agents might have some secondary sedative effect. Internationally there is a range of different methods of managing patients' sedation needs. Common elements in this process include the prescription (order) of sedation, including details such as drug and route, made by the physician or nurse practitioner; and use of a formal sedation scale to determine how sedated the patient is, although many different scales are in use. Less consistent elements include whether a target of how awake the patient should be (this may be a descriptor of a score on a sedation scale) is specified, whether nurses or other healthcare professionals can titrate the sedative administration rate, including ceasing it, and whether daily interruptions are used.

Description of the intervention

Various strategies have been proposed as methods to improve sedation management of critically ill patients. These strategies have included use of an appropriate sedation assessment instrument (Curley 2006; Ely 2003; Riker 1999); use of a sedation guideline, algorithm or protocol to guide assessment and therapy (Jacobi 2002; Sessler 2009); implementation of daily sedation interruptions (Kress 2000); use of minimal levels of sedation and regular assessment of sedation and analgesia requirements (Schweickert 2008). Despite a core component of many of these recommendations being the use of an algorithm or protocol, there is evidence to suggest that sedation guidelines remain poorly implemented, with less than 50% of critical care units in Canada, USA and Denmark indicating such use (Schweickert 2008). This lack of implementation may be due to the inconsistent results that have been identified in the studies examining the effect of protocol-directed sedation (Brook 1999; Bucknall 2008; De Jonghe 2005; Elliott 2006; Quenot 2007).

Protocol-directed sedation is ordered by a physician, contains guidance regarding sedation management, and is implemented by nurses, pharmacists or other members of the healthcare team. Selection of the most appropriate sedative agent, as well as when to commence, increase, decrease or cease administration of the agent, is based on patient assessment, usually with the aid of a sedation scale. Protocols may include an analgesic component (Brook 1999). Protocol-directed sedation is distinct from, but related to, protocol-directed weaning, which is specifically directed towards limiting the duration of mechanical ventilation; this topic is the subject of a separate Cochrane Review (Blackwood 2014).

How the intervention might work

Use of a protocol to guide sedation practices may improve sedation by incorporating regular patient assessment with planned changes to sedative or analgesic agents, or both. There is widespread evidence of international variation in sedation assessment and management practices (Mehta 2009; O'Connor 2009; Richards-Belle 2016). The potential to reduce the individual clinician variation is significant, with management based on standardized assessment practices.

Why it is important to do this review

Use of sedation protocols has been proposed as a potential strategy to improve sedation practices in intensive care with resultant reduced duration of mechanical ventilation and ICU length of stay, with the potential to affect patient mortality. Despite widespread use, there is mixed evidence as to their effectiveness.

OBJECTIVES

To assess the effects of protocol-directed sedation management compared to usual care on the duration of mechanical ventilation, intensive care unit (ICU) and hospital mortality and other patient outcomes in mechanically ventilated ICU adults and children.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) and quasi-RCTs published in any language. We defined a RCT as a study in which patients were allocated to treatment groups based on a random or quasi-random method (e.g. using random number tables, hospital number, date of birth).

Types of participants

We included all intensive care unit (ICU) adult and paediatric patients who were mechanically ventilated (via endotracheal or

tracheostomy tube). If eligible studies had included both patients who met the above criteria and those who did not, we would have excluded the data unless the subpopulations were reported, or able to be obtained, separately.

Types of interventions

The target intervention was protocol-directed sedation management. We compared this with non-protocol-directed sedation management.

We defined protocol-directed sedation as sedation directed by a protocol or algorithm that was ordered by a medical officer, contained guidance regarding sedation management, and was implemented by nurses, pharmacists or other members of the healthcare team with sedation increased or decreased based on patient assessment. The guidance regarding sedation management consisted of a series of decision points or decision algorithms that assisted clinicians to make decisions regarding increasing, decreasing or maintaining current sedation levels. Protocols included provision for administration of analgesics in addition to sedative agents. Medical officers may have continued to be involved in sedation assessment and management beyond the point of ordering the sedation protocol, but we excluded any protocol that required physician approval for changes in amounts of sedation. The essential element of protocol-directed sedation was that other members of the healthcare team could alter the level of sedation being administered without consulting with a medical officer.

We defined usual care as physician-led sedation management of mechanically ventilated patients according to local practice, where no specific strategies were implemented to change the level of sedation that was administered to reduce the duration of mechanical ventilation. Sedative agents may or may not have been different to those used in the intervention; importantly the intervention was not about the agents that were used but how they were used.

Types of outcome measures

Primary outcomes

1. Duration of mechanical ventilation, measured in hours for the entire duration of the first ICU stay for each patient
2. ICU and hospital mortality

Secondary outcomes

1. ICU length of stay
2. Hospital length of stay
3. Total dose of sedation (mg)
4. Adverse events within ICU (self-extubation or reintubation)
5. Incidence of delirium in ICU
6. Memory function after hospital discharge, using any validated measure
7. Psychological recovery after hospital discharge, using any validated measure
8. Cognitive recovery after hospital discharge, using any validated measure
9. Quality of life after hospital discharge, using any validated measure
10. Incidence of tracheostomy within ICU, using any validated measure

Where a study reported both ICU and hospital mortality, the ICU deaths were also included in hospital mortality. Similarly, where a study reported both ICU and hospital length of stay, the days spent in ICU were also included in hospital length of stay.

Search methods for identification of studies

Electronic searches

We identified RCTs through literature searching with systematic and sensitive search strategies, as outlined in Chapter 6.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We did not apply restrictions to language or publication status. The original search was run in November 2013 (Aitken 2015), and for that search, we chose the inception date of 1990 because no sedation protocols existed before this time.

We searched the following databases for relevant trials.

1. Cochrane Central Register of Controlled Trials (CENTRAL; December 2017).
2. MEDLINE (Ovid SP, 1990 to December 2017).
3. Embase (Ovid SP, 1990 to December 2017).
4. CINAHL (EBSCOhost, 1990 to December 2017).
5. LILACS (BIREME, 1990 to December 2017).

We developed a subject-specific search strategy in MEDLINE and used that as the basis for the search strategies in the other databases listed. Where appropriate, we expanded the search strategy with search terms for identifying RCTs. All search strategies can be found in Appendix 1.

We handsearched relevant journals (including online journals), such as *American Journal of Respiratory & Critical Care Medicine*, *Critical Care Medicine*, *Intensive Care Medicine*, *Critical Care*, *American Journal of Critical Care and Australian Critical Care* (1990 to June 2017).

We searched the following websites in July 2017 for relevant ongoing trials.

1. International Clinical trials registry (www.who.int/trialsearch).
2. International Standard Randomized Controlled Trials (www.controlled-trials.com/isrctn).
3. Country-specific trial websites for the UK, South Africa, India, Hong Kong, China, and Australia and New Zealand.

Searching other resources

1. We scanned the reference lists and citations of included trials and any relevant systematic reviews identified for further references to additional trials.
2. When necessary, we contacted trial authors for additional information.

Data collection and analysis

Selection of studies

Two review authors (LA and BK) independently reviewed all titles and decided on the inclusion of studies based on selection criteria (see Appendix 2). We resolved differences and avoided conflicts by

consulting a third review author (MM). We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009).

Data extraction and management

We extracted standardized data from each study using a data extraction form (see Appendix 3). Two review authors (LA, TB, MM or EB) independently extracted data for all studies, while ensuring that data extraction processes avoided conflict of interest due to authorship of one included study (Bucknall 2008). SK and LA transformed data from the clustered trial study included in the update. We resolved any disagreements by discussion; if required, we could have consulted with an alternative review author, but this was not required. If a study had insufficient data to complete data extraction or if we required data clarification, we contacted the authors of the study. We considered the studies to have sufficient data if at least one of the listed outcomes (either primary or secondary) was reported.

Assessment of risk of bias in included studies

Two review authors (LA, TB, MM or EB) independently assessed the methodological quality of each eligible trial. We resolved disagreements by discussion. Where potential conflicts of interest existed, for example authorship of an included study, we excluded the relevant author from the process and involved an alternate author. We performed the assessment as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using a quality assessment form (see Appendix 4).

We assessed the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other potential sources of bias.

We considered a trial as having a high risk of bias if one or more of the assessment domains (listed above) was rated as high risk or unclear.

We noted judgements based on the risk of selective reporting in the 'Risk of bias' tables that follow each study in the Characteristics of included studies table. We generated a 'Risk of bias' graph and a 'Risk of bias' summary. We also reported the risk of selective outcome reporting in the results under Assessment of risk of bias in included studies.

Measures of treatment effect

Subject to the absence of clinical heterogeneity, we undertook an analysis using Review Manager 5 software (Review Manager 2014). For continuous data, we used the mean difference (MD), or standardized mean difference (SMD), and 95% confidence interval (CI) for summary statistics (hospital and ICU length of stay, duration of mechanical ventilation) wherever possible. We found the data to be skewed and, due to the unavailability of some source data, we were unable to transform the data for analysis. For dichotomous data, we used risk ratio (RR) and 95% CI (e.g. mortality, tracheostomy). We would have calculated the number needed to treat for an additional beneficial outcome (NNTB) with 95% CI, if we had identified significant differences between the intervention and control groups.

Unit of analysis issues

All data extracted reflected the original allocation group with three of the studies specifying the use of intention-to-treat analysis (Brook 1999; Bucknall 2008; Curley 2015). There was no evidence of multiple observations or outcome measurements in any of the included studies. There was no evidence of multiple observations for the same outcome measurement and all outcome measurements were taken at the same time point in both studies. The duration of mechanical ventilation was measured on the same group of patients throughout their ICU stay. To avoid unit-of-analysis error with data, we transformed a cluster trial (data from the Curley 2015 study) to its effective sample size by calculating the design effect using the Rao 1992 calculation that uses the average cluster size and the intraclass coefficient (ICC), either from the actual study or a reliable estimate from previous publications. We calculated the design effect for the trial as a whole and used this figure to then adjust both the number of participants and the number experiencing the event. For continuous data only the sample size was reduced; means and standard deviations remained unchanged.

Dealing with missing data

Published study reports for two studies identified complete data for all included participants (Brook 1999; Bucknall 2008); 15 of 111 (13.5%) intervention participants in the Mansouri 2013 study were withdrawn due to protocol violation; and 10 of 1235 intervention participants (< 1%) in the Curley 2015 paediatric study, had consent for the protocol and data collection withdrawn by parents. No imputation for missing data was undertaken in this review. We contacted the lead authors of the Curley 2015 and Mansouri 2013 studies to retrieve original mean and standard deviation data as only medians and interquartile ranges were reported in publications.

Assessment of heterogeneity

We assessed clinical heterogeneity for key participant and sedation protocol characteristics. Study cohorts were considered sufficiently similar for participant and intervention characteristics to suggest data could potentially be pooled for statistical analysis. We assessed statistical heterogeneity using the I^2 statistic. Where this analysis suggested statistical heterogeneity was moderate or greater, we noted this concern.

Assessment of reporting biases

We had planned that if sufficient studies (i.e. at least 10) met the criteria to be included in the analysis, we would construct a funnel plot to explore the symmetry of the intervention effects reported by the studies to assess for publication bias. Given that the search identified only four studies to include in the analysis, the exploration of reporting bias was not possible.

Data synthesis

We had planned that if the studies were sufficiently homogenous, we would conduct a meta-analysis using a fixed-effect model. Where heterogeneity did exist, we used a random-effects model. Analyses were considered significant at the alpha = 0.05 level. We

assessed estimates of precision by interpretation of CIs, such as widths, overlapping and inclusion of the null hypothesis.

Subgroup analysis and investigation of heterogeneity

Intensive care patients were a heterogeneous group. We had planned to undertake subgroup analyses to examine the impact of the intervention on medical, surgical and trauma intensive care patients, or in units with 1:1 nurse:patient ratio during usual care versus units with 1:2 (or greater) nurse:patient ratio during usual care, or in patients ventilated via an endotracheal tube versus a tracheostomy tube, or the influence of age group as well as any differential effect of nurse-led protocols versus protocols led by other members of the healthcare team (e.g. respiratory therapists). Participants in the study by Brook 1999 were admitted to a medical ICU while participants in the studies by Bucknall 2008 and Mansouri 2013 were admitted to a general ICU incorporating medical as well as surgical and trauma patients. Participants in the study by Curley 2015 were paediatric patients. Given the small number of studies and limited variation in the included participants, we could only undertake limited subgroup analysis of the effects of paediatric versus adult patients.

Sensitivity analysis

We had planned to perform sensitivity analyses to test how sensitive the data were to reasonable changes in the assumptions that were made and in the methods used for combining the data. We planned to test the robustness of the evidence by sensitivity analysis according to randomization (randomized or quasi-randomized) and risk of bias (high, low or unclear). Given all aspects of the risk of bias were rated the same and used similar methods for randomization, we could not undertake sensitivity analyses. Analysis of data with and without data from single cluster trials also did not change findings.

'Summary of findings table' and GRADE

We used the principles of the GRADE system to assess the quality of the body of evidence associated with specific outcomes listed below (Guyatt 2008).

1. Duration of mechanical ventilation.
2. ICU mortality.
3. Hospital mortality.
4. Length of ICU stay.
5. Length of hospital stay.
6. Adverse events within ICU (incidence of self-extubation, incidence of reintubation).
7. Incidence of tracheostomy.

We constructed a 'Summary of findings' table using the GRADE software (GRADEpro GDT). The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence considers within-study risk of bias (methodological quality), the directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias.

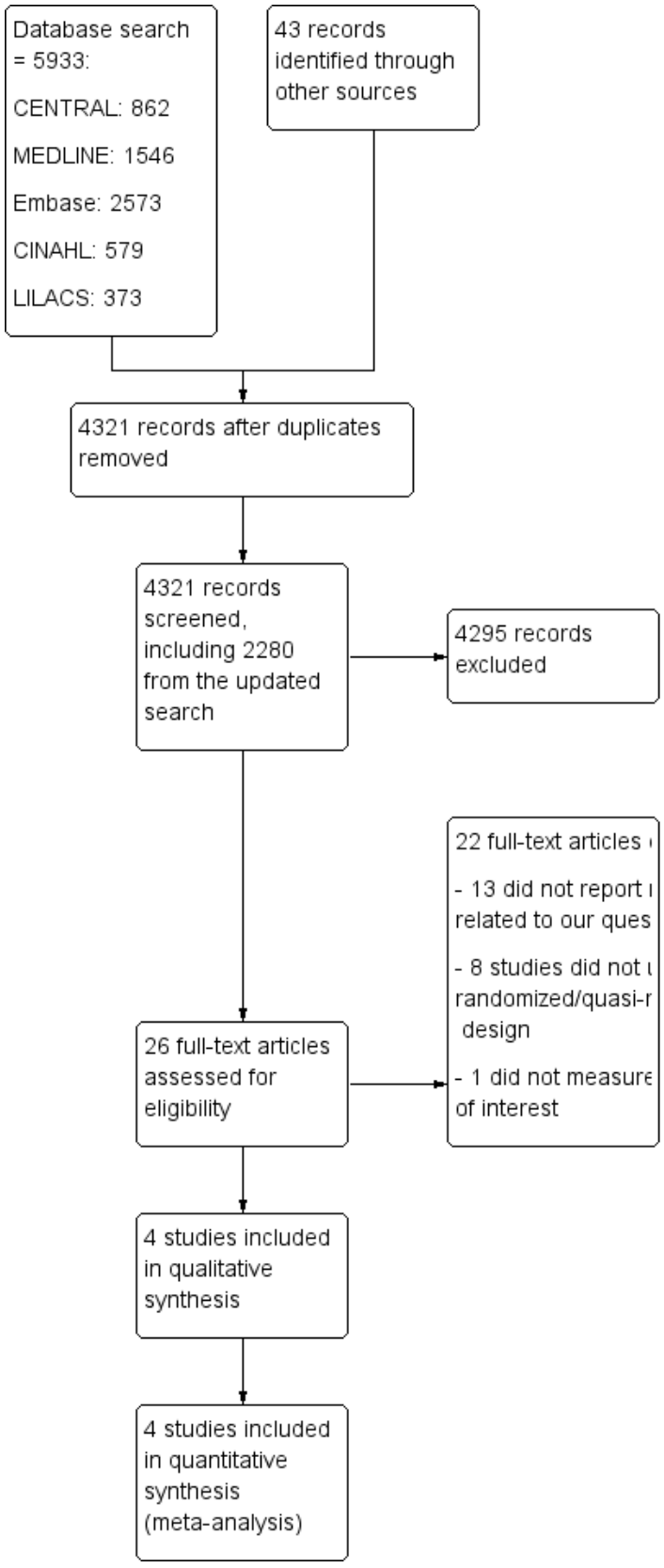
RESULTS

Description of studies

Results of the search

The results of the search and selection of studies are summarized in the PRISMA study flow diagram (Figure 1). Through both the original search (Aitken 2015), and this update we identified 5933 records through database searching and 43 studies through manual search processes, although all these studies had been identified in the database search. The total number of records was reduced to 4321 records after we removed duplicates. We identified four studies of interest (Brook 1999; Bucknall 2008; Curley 2015; Mansouri 2013). Two of these studies were included in the previous version of this review (Brook 1999; Bucknall 2008), one was awaiting classification (Mansouri 2013), and one was newly identified (Curley 2015).

Figure 1. Study flow diagram.



Included studies

We included four studies (see Characteristics of included studies table; Brook 1999; Bucknall 2008; Curley 2015; Mansouri 2013). Three studies were similar in design and examined the impact of protocol-directed sedation on a range of outcomes including duration of mechanical ventilation, mortality, ICU and hospital length of stay, and some adverse events in adult patients (Brook 1999; Bucknall 2008; Mansouri 2013). The fourth study (Curley 2015), was a large cluster-randomized controlled trial (cluster-RCT) that examined similar outcomes in the paediatric intensive care unit (ICU) population.

Population and setting

Brook 1999 enrolled 332 participants (321 included in analysis) from a single 19-bed medical ICU within a university-affiliated urban teaching hospital in the USA, with data collected in 1997 to 1998. Participants were older than 17 years and received mechanical ventilation. Participants were excluded if they were temporarily admitted (for less than 24 hours) to the medical ICU while they were awaiting admission to the surgical ICU. In contrast, Bucknall 2008 enrolled 316 participants (312 included in final analysis) from a 24-bed mixed ICU in a major Australian metropolitan university-associated teaching hospital. Participants were adults who were mechanically ventilated. Participants were excluded if they were admitted to the ICU following cardiac surgery (due to expected brief admission) or if they were readmitted to the ICU after being in the study previously. Both studies were in closed ICUs with medical care provided by critical care specialists. Mansouri 2013 enrolled 216 participants (201 included in final analysis) from two mixed medical-surgical ICUs in a university hospital in Iran. Participants were adults who were mechanically ventilated. Participants were excluded if they had an ICU stay less than 24 hours, expected to die within 48 hours, received muscle relaxants or anticonvulsant drugs, had psychological illness, upper extremity paralysis or were immobilized in a cast. Curley 2015 enrolled 2459 paediatric participants (2449 included in final analysis) from 31 paediatric ICUs across the USA. ICU inclusion criteria required that the unit have no sedation protocol in place, have leadership support for the study who agreed to the study design and be able to enrol at least three participants per month. Patient-level criteria included being intubated and mechanically ventilated, be more than two weeks of age but less than 18 years of age and the primary reason for intubation be acute lung disease. Participants were excluded if their length of ventilation was unlikely to be altered by sedation management or if they had any of a series of specific diagnoses (e.g. cyanotic heart disease, primary pulmonary hypertension etc.).

Interventions and comparisons

Three studies were single-centre, patient-level RCTs (Brook 1999; Bucknall 2008; Mansouri 2013), while one study was a multicentre, cluster-level RCT (Curley 2015). The interventions were generally similar, with Bucknall 2008 indicating they modelled their intervention on that reported by Brook 1999, while Mansouri 2013 developed their intervention locally but indicated it was consistent with international guidelines (Barr 2013). The intervention tested in the study by Curley 2015 has many similar features, although places more emphasis on daily team discussion of the patient's trajectory of illness and associated sedation management. In all studies, nurses used a structured approach for assessment to determine whether analgesics or sedatives (or both) were required by the patient, then administered prespecified medications according to their ongoing assessment. Differences in the medications used existed, with Brook 1999 using diazepam, midazolam, fentanyl and morphine, Bucknall 2008 using midazolam, propofol and morphine, Mansouri 2013 using midazolam, propofol, haloperidol, morphine, fentanyl, sufentanyl and acetaminophen, and Curley 2015 primarily using midazolam, lorazepam, morphine and fentanyl.

The most significant difference between the studies was the usual method of providing sedation-related aspects of care to patients in each of the study sites. In the single-centre USA study, all aspects of sedation were ordered by the treating physicians and nurses could not make changes without a physician's written or verbal order (Brook 1999). In the single-centre Australian study, ICU medical staff prescribed the type of sedation medication and dose limits for infusion and boluses, with each patient's ICU nurse free to assess, titrate and manage sedation, including the ceasing of sedation, within those limits (Bucknall 2008). In the single-centre Iranian study, pain and sedation were managed according to as-needed physician orders but no regular assessment for pain, sedation or delirium were conducted (Mansouri 2013). In the multicentre USA study conducted in paediatric ICUs, sedation was selected, prescribed and titrated by each local medical team (Curley 2015).

Excluded studies

We excluded non-RCTs and studies that did not examine outcomes of interest (see Excluded studies). We identified 4321 records after we had removed duplicates. We retrieved 26 full-text articles. We excluded nine of these as they did not meet the criteria for inclusion in this review (Arias-Rivera 2008; Brattebo 2002; Bugedo 2013; De Jonghe 2005; Elliott 2006; Gaillard-Le Roux 2017; Hahn 2013; Quenot 2007; Tobar 2008).

We excluded eight, of the nine, studies as, although they addressed the question of our review, they did not use a randomized or quasi-randomized design and we excluded one study as it did not measure an outcome of interest. The Characteristics of excluded studies tables provides details of studies that did address the question of our review but did not use a randomized or quasi-randomized design.

Studies awaiting classification

There are no studies awaiting classification.

Ongoing studies

We identified no ongoing studies.

Risk of bias in included studies

We analysed seven domains of potential risk of bias for the included studies (Figure 2; Figure 3). We rated performance bias at high risk for three studies (Brook 1999; Bucknall 2008; Mansouri 2013), and unclear risk for the remaining study (Curley 2015), while selection bias due to random sequence generation was unclear for three studies (Brook 1999; Curley 2015; Mansouri 2013), and low for the other study (Bucknall 2008). We rated selection bias due to allocation concealment as low for two studies (Brook 1999; Bucknall 2008), unclear for one study (Mansouri 2013), and high for the remaining study (Curley 2015). We generally rated other prespecified risks at low risk of bias. We rated two studies as having an unclear risk of reporting bias (Brook 1999; Mansouri 2013), with

two studies having a low risk of reporting bias (Bucknall 2008; Curley 2015). We judged three studies as having an unclear risk of other bias (Brook 1999; Bucknall 2008; Mansouri 2013), with one study having a low risk of other bias (Curley 2015). There was a lack of description of usual care and nurse:patient ratios in two studies (Brook 1999; Mansouri 2013), with variable nurse:patient ratios in one study (Curley 2015). Three studies had potential for contamination between the two groups (Brook 1999; Bucknall 2008; Mansouri 2013).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

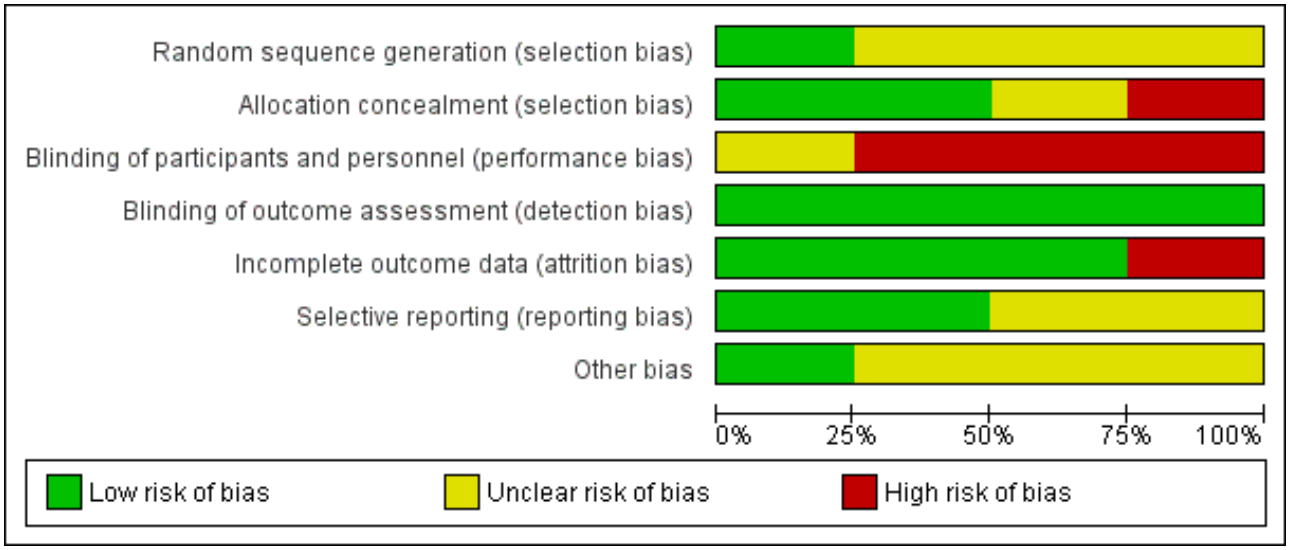
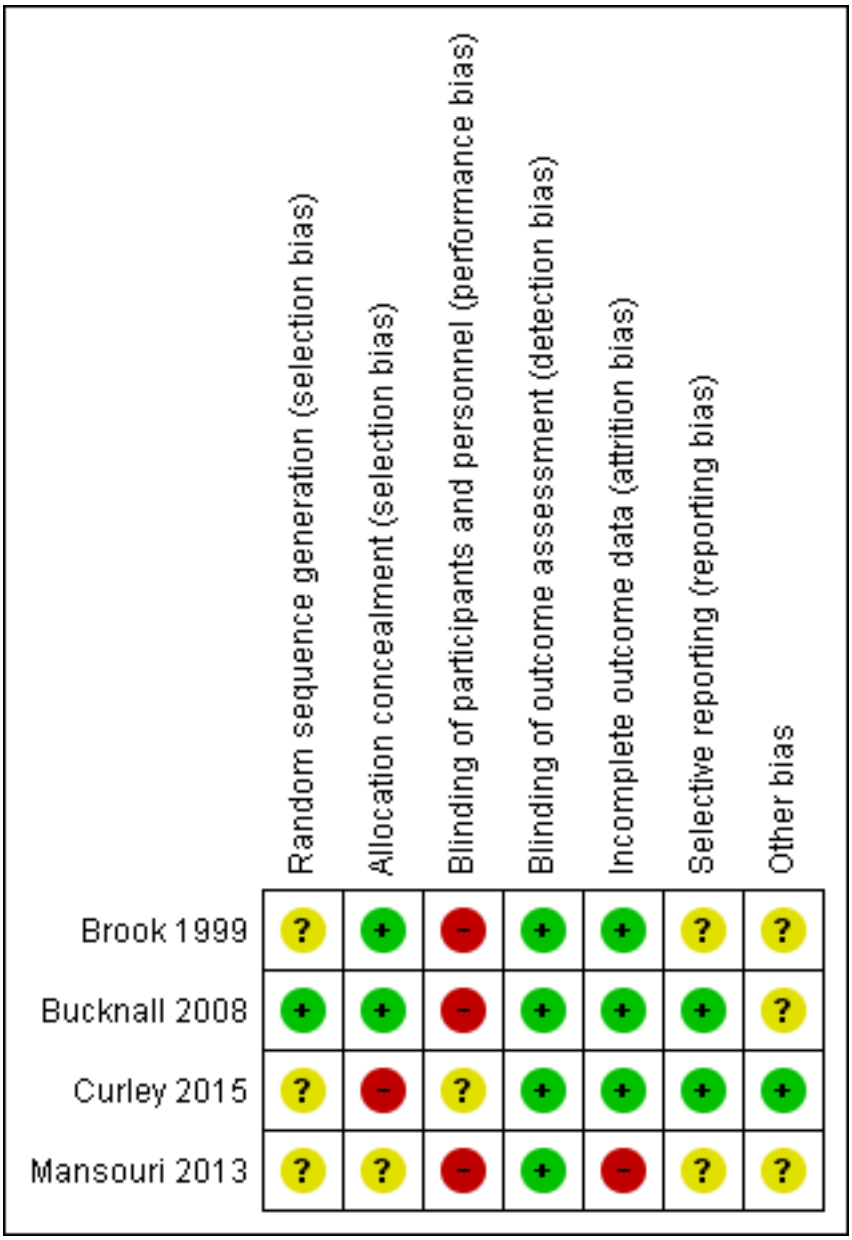


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All studies used randomization at either the patient or unit level and two studies had effective allocation concealment (Brook 1999; Bucknall 2008). One study used computer-generated random sequence (Bucknall 2008); however, the method of random sequence generation in two studies was not described (Brook 1999; Mansouri 2013). In the multicentre cluster-randomized study, no detail regarding the random sequence generation was provided and no information was provided regarding how allocation was concealed (Curley 2015).

Blinding

The intervention being examined, use of protocol-directed sedation, meant that it was not feasible to blind the study participants, clinicians and some study personnel. Despite this, we rated studies as having a low risk of detection bias given the objective nature of the outcomes measured in the studies (duration of mechanical ventilation, length of stay, mortality, incidence of tracheostomy) (Brook 1999; Bucknall 2008; Curley 2015; Mansouri 2013).

Incomplete outcome data

Where complete outcome data were not available for all participants, the reason for the lack of data was provided in three studies and rates of attrition were low, resulting in a rating of low risk of attrition bias (Brook 1999; Bucknall 2008; Curley 2015). In the remaining study the reason for incomplete outcome data was not provided, resulting in a rating of high risk of attrition bias (Mansouri 2013).

Selective reporting

We rated two studies as having an unclear risk of selective reporting bias, with results relating to all specified outcomes being reported (Brook 1999; Mansouri 2013). We rated two studies as having a low risk of selective reporting bias, primarily due to being registered on a relevant trial website (www.ClinicalTrials.gov; NCT00202319, Bucknall 2008 and NCT00814099, Curley 2015). One study was not registered or the protocol published (Brook 1999), however this study was conducted prior to this being usual practice.

Other potential sources of bias

Three studies had an unclear risk of bias due to other potential sources. Of note, usual care was not described well by Brook 1999 or Mansouri 2013. It was unclear if standard management practices (mode of mechanical ventilation, physiotherapy, suctioning, repositioning, investigations outside the ICU, need for physical restraints) or nurse:patient ratios were equally applied to both groups. While Bucknall 2008 provided a description of usual care for general management and specific sedation management, some associated aspects of care, such as physiotherapy, suctioning, repositioning, investigations outside the ICU and need for physical restraints, were not provided. Extensive details of other aspects of care, such as staffing levels, experience of staff and unit-based practices were provided in supplementary materials attached to the Curley 2015 publication. If standard management practices differed between groups, there was a risk of bias.

In addition, a potential for contamination between the two groups existed in three studies as participants were cared for in the same ICU at the same time and care of control group participants was directed by physicians in line with usual local practice and individual preferences (Brook 1999; Bucknall 2008; Mansouri 2013). It is possible that the principles of protocol-directed care could have been partially applied to the control group.

Effects of interventions

See: **Summary of findings for the main comparison** Protocol-directed sedation management compared with usual care for sedation management in mechanically ventilated intensive care unit patients

Primary outcomes

1. Duration of mechanical ventilation, measured in hours for the entire duration of the first ICU stay for each patient

Four included studies (Brook 1999; Bucknall 2008; Curley 2015; Mansouri 2013), 3283 participants (or adjusted sample n = 2210); reported duration of mechanical ventilation in a form that could be used for meta-analysis. When we pooled data to analyse the mean difference (MD) receiving mechanical ventilation (MD -28.15 hours, 95% confidence interval (CI) -69.15 to 12.84) comparing management with protocol-directed sedation with usual care, the test for heterogeneity was substantial (Tau^2 = 1402.95; Chi^2 = 20.46, degrees of freedom (df) = 3 (P = 0.0001); I^2 = 85%; Analysis 1.1). Such high heterogeneity suggested that the studies were very dissimilar, and may reflect the differing nurse:patient ratios present in usual care within the study environments (see Characteristics of included studies table). The measure of heterogeneity was similar when studies including adult patients only were examined (Tau^2 = 3303.43; Chi^2 = 20.25, df = 2; P < 0.0001; I^2 = 90%). Interpretation of these results should proceed with caution given this high level of statistical heterogeneity. We assessed the overall quality of evidence for this outcome as low (Summary of findings for the main comparison).

2. ICU and hospital mortality

Only two studies reported ICU mortality data (Bucknall 2008; Mansouri 2013), 513 participants. Forty-four of 249 (18%) participants receiving protocolized sedation and 57 of 264 (22%) participants receiving usual care died in the ICU. The combined ICU mortality outcome, with 513 participants, was not significantly different between the protocol-directed sedation and usual care groups (risk ratio (RR) 0.77, 95% CI 0.39 to 1.50; heterogeneity Tau^2 = 0.16; Chi^2 = 3.06, df = 1; P = 0.08; I^2 = 67%; Analysis 1.2). We assessed the overall quality of evidence for this outcome as low (Summary of findings for the main comparison). Three studies reported hospital mortality data (Brook 1999; Bucknall 2008; Curley 2015), 3082 participants (or adjusted sample n = 2008). The mortality rate varied between the adult and paediatric studies, with 88 of 315 (28%) adult participants receiving protocolized sedation and 92 of 318 (29%) adult participants receiving usual care dying during their hospital stay (Brook 1999; Bucknall 2008). In contrast, 67 of 1225 (5%) (or adjusted statistic 38 of 688 (5%)) paediatric participants receiving protocolized sedation and 88 of 1224 (7%) (or adjusted statistic 49 of 687 (7%)) paediatric participants receiving usual care died during their hospital stay (Curley 2015). The combined hospital mortality outcome, with 3082 participants (adjusted sample n = 2008), was not significantly different between the protocol-directed sedation and usual care groups (RR 0.90, 95% CI 0.72 to 1.13; heterogeneity: Tau^2 = 0.00; Chi^2 = 2.22, df = 2 (P = 0.33); I^2 = 10%; Analysis 1.3). This level of heterogeneity again suggests the two cohorts may have important differences as outlined above, although it was not substantial. We assessed the overall quality of evidence for this outcome as low (Summary of findings for the main comparison).

Secondary outcomes

1. ICU length of stay

Four included studies (Brook 1999; Bucknall 2008; Curley 2015; Mansouri 2013), 3128 participants (or adjusted sample n = 2123) reported length of ICU stay. When we pooled data to analyse the MD in length of ICU stay (MD -1.70 days, 95% CI-3.71 to 0.31) comparing management with protocol-directed sedation with usual care, the test for heterogeneity was substantial (Tau^2 = 3.32; Chi^2 = 17.04, df = 3 (P = 0.0007); I^2 = 82%; Analysis 1.4). Such high heterogeneity suggested that the four studies were very dissimilar, and may reflect the differing nurse:patient ratios present in usual care within the study environments. The assessment of heterogeneity was similar when studies including adult patients only were examined (Tau^2 = 6.13; Chi^2 = 16.80, df = 2; P = 0.0002; I^2 = 88%). Interpretation of these results should proceed with caution given this high level of statistical heterogeneity. We assessed the overall quality of evidence for this outcome as low (Summary of findings for the main comparison).

2. Hospital length of stay

Three included studies, 2927 participants (or adjusted sample n = 1922) reported hospital length of stay (Brook 1999; Bucknall 2008; Curley 2015). The combined MD in hospital length of stay differed significantly, with participants in the protocolized sedation group having significantly shorter hospital stays than participants in the usual care groups (MD -3.09 days, 95% CI -5.08

to -1.10; heterogeneity: Tau² = 0.07; Chi² = 2.03, df = 2 (P = 0.36); I² = 2%; Analysis 1.5). When the one study that used cluster-randomization in the paediatric population was removed, 633 participants reported hospital length of stay; the combined MD in hospital length of stay was not significantly different between the protocol-directed sedation and usual care groups (MD-3.78, 95% CI -8.54 to 0.97; heterogeneity Tau² = 4.83; Chi² = 1.67, df = 1, P = 0.20; I² = 40%). We assessed the overall quality of evidence for this outcome as moderate (Summary of findings for the main comparison).

3. Total dose of sedation (mg)

Only one study reported sedation doses (Curley 2015). While overall opioid doses were not statistically different between groups with regards to mean daily dose, peak daily dose or cumulative dose, patients in the protocol-directed group had fewer days of exposure to opioids, median 9 days versus 10 days in the control group; hazard ratio (HR) for days with no exposure, 1.27, 95% CI 1.05 to 1.54; P = 0.01. For benzodiazepines, again, mean daily, peak daily and cumulative doses were not statistically different between groups. Days of benzodiazepine exposure were not reported. Of the secondary sedatives reported, there was significantly different dosing between groups for dexmedetomidine (protocol-directed 287/1225 (23%) versus usual care 596/1224 (49%), P < 0.001); methadone (protocol-directed 148/1224 (12%) versus usual care 368/1224 (30%) P < 0.001), and chloral hydrate (protocol-directed 34/1225 (3%) versus usual care 181/1224 (15%) P = 0.01). No confidence intervals were reported for these statistics.

4. Adverse events within ICU (self-extubation or reintubation)

The studies reported few adverse event data. One study (321 participants) reported reintubation rates (RR 0.65, 95% CI 0.35 to 1.24; Analysis 1.7; Brook 1999); the RR of 0.65 suggests protocol-directed sedation compared to usual care shows a trend towards fewer reintubations, but this is not significant. Two studies (2761 participants or adjusted sample of n = 1687) reported self-extubation data, however the combined data were not significantly different between the two groups (RR 0.88, 95% CI 0.55 to 1.42; heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 1 (P = 0.47); I² = 0%; Analysis 1.6; Bucknall 2008; Curley 2015); again the RR of 0.88 suggests protocol-directed sedation compared to usual care shows a trend towards fewer self-extubations, but this is not significant. Although these two outcomes are similar, some participants who self-extubate will not require reintubation, therefore self-extubation rates would normally be higher than reintubation rates. In these two studies, Bucknall 2008 and Curley 2015 reported self-extubation rates of 1% or lower in each group, while Brook 1999 reported reintubation rates of 6% to 13% in their two groups; this suggests there was substantial heterogeneity between the various cohorts for these adverse events, possibly related to the differing nurse:patient ratios and different age profiles previously described. We rated the overall quality of evidence for self-extubation as high and for reintubation as low (Summary of findings for the main comparison).

5. Incidence of delirium in ICU

We found no studies reporting incidence of delirium.

6. Memory function after hospital discharge, using any validated measure

We found no studies reporting memory function.

7. Psychological recovery after hospital discharge, using any validated measure

We found no studies reporting psychological recovery.

8. Cognitive recovery after hospital discharge, using any validated measure

We found no studies reporting cognitive recovery.

9. Quality of life after hospital discharge, using any validated measure

We found no studies reporting quality of life.

10. Incidence of tracheostomy within ICU, using any validated measure

The incidence of tracheostomy was reported in three included studies (Brook 1999; Bucknall 2008; Curley 2015), 3082 participants (or adjusted sample n = 2008). When we pooled data to analyse the frequency of tracheostomy (RR 0.67, 95% CI 0.35 to 1.30) comparing management with protocol-directed sedation with usual care, the test for heterogeneity was substantial (Tau² = 0.22; Chi² = 5.89, df = 2 (P = 0.05); I² = 66%; Analysis 1.8). Such high heterogeneity suggested that the studies were very dissimilar, and may reflect the differing nurse:patient ratios present in usual care within the study environments. The measure of heterogeneity was similar when studies including adult patients only were examined (Tau² = 0.32; Chi² = 4.16, df = 1; P = 0.04; I² = 76%). Interpretation of these results should proceed with caution given this high level of statistical heterogeneity. We rated the overall quality of evidence for this outcome as low (Summary of findings for the main comparison).

DISCUSSION

Summary of main results

We identified four RCTs with 3323 participants (3283 included in analysis) assessing our primary outcomes of duration of mechanical ventilation and mortality. Brook 1999 reported a reduction in duration of mechanical ventilation and no difference in hospital mortality with protocol-directed sedation in a single-centre, patient randomized study conducted in the USA, Bucknall 2008 reported no difference in duration of mechanical ventilation, intensive care unit (ICU) or hospital mortality in an Australian, single-centre, patient randomized study, Mansouri 2013 reported reductions in both duration of mechanical ventilation and ICU mortality in a single-centre, patient randomized study conducted in Iran, and Curley 2015 reported no difference in duration of mechanical ventilation or hospital mortality in a cluster-randomized, paediatric study conducted in the USA. When we pooled data, both duration of mechanical ventilation and ICU and hospital mortality did not differ between participants who received protocol-directed sedation and participants who received usual care. Significant heterogeneity suggested the cohorts were very dissimilar for the outcome of duration of mechanical ventilation, therefore interpretation of results should proceed with caution.

Secondary outcomes that were reported in two or more studies included ICU and hospital length of stay, and incidence of tracheostomy or self-extubation. There was no difference in duration of ICU length of stay or incidence of tracheostomy or self-extubations between participants who received protocol-directed sedation and participants who received usual care. Hospital

length of stay was significantly reduced in patients who received protocol-directed sedation compared to those who received usual care. Significant heterogeneity suggested the cohorts were very dissimilar for the outcomes of ICU length of stay and incidence of tracheostomy, therefore interpretation of results should proceed with caution.

Overall completeness and applicability of evidence

The four studies included in this systematic review reported data regarding our primary outcomes; however, data relating to only a few of our secondary outcomes were reported. Importantly, no study examined the relationship between protocol-directed sedation and post-ICU outcomes such as memory function, psychological and cognitive recovery, and quality of life. This is despite recognition that sedation practices are likely to influence these long-term outcomes (Barr 2013).

Despite similar participant and intervention characteristics between three of the four studies included in this review, substantial heterogeneity existed for most outcomes, limiting our ability to interpret the meta-analyses in a meaningful way. This heterogeneity may be the result of studies being conducted in different countries, different decades and different age groups of participants. With trials conducted in a variety of geographic locations and across different times, this may have resulted in substantial differences in important related areas of practice, such as usual sedation practices and agents, patterns and modes of mechanical ventilation, mobilization practices and other aspects of intensive care that affect the identified outcomes. One aspect of critical care organization that differed between the various settings was the usual nurse:patient ratio, with each nurse:patient ratio varying from one:one in some settings to one:two or one:three in other settings; this has the potential to affect aspects of care, such as how much patient agitation might be tolerated. Details regarding usual care are essential in the publication of studies that deal with a complex area of practice, as there are many variations across time and location that are essential to understand in order to determine applicability of evidence. The differences in age of study participants, with three studies being conducted in adult patients and one study conducted in paediatric patients may result in important differences in physiology, pathophysiology and sedation-related aspects of care; greater numbers of studies in both patient age groups would allow important subgroup analysis.

Quality of the evidence

The methodological quality of the studies included in this review was moderate, and the quality of the overall evidence was low. We only included four studies and they frequently had conflicting results, resulting in wide confidence intervals for some outcomes. This heterogeneity between the studies limits the overall quality of this review. Sources of heterogeneity are discussed when considering Agreements and disagreements with other studies or reviews and relate to patient, staffing and clinical practice issues. Furthermore, although we generally rated studies as having a low risk of detection and attrition bias and some aspects of selection bias, a number of the studies had unclear or high risks of bias related to other aspects of selection, reporting and performance. Due to the nature of the intervention, it was not possible to blind participants or clinicians. Importantly, only one study was conducted in the paediatric population (Curley 2015), and that same study used cluster-randomization in contrast to all other studies using individual-randomization in the adult population. When we conducted a sensitivity analysis to assess the impact of this study on the results, we did not identify any changes in any outcomes, apart from hospital length of stay, where we no longer identified a significant difference when we removed the Curley 2015 study.

Potential biases in the review process

Clearly described procedures were followed to minimize potential bias in the review process. We conducted a careful literature search, and used transparent and reproducible methods. Where a review author was involved in an included study (Bucknall 2008), we had alternative authors (LA and MM) extract the information.

Agreements and disagreements with other studies or reviews

The effect of the use of protocol-directed sedation on patient outcomes has been of interest for several years and, while it has not been the subject of any other reviews, it has been the subject of additional, non-randomized studies. Consistent with the findings of the studies included in this review (Brook 1999; Bucknall 2008; Curley 2015; Mansouri 2013), findings from non-randomized studies have generally been conflicting. One non-randomized study conducted in Australia found no benefit and, in fact, an increase in the duration of ICU length of stay with the implementation of protocol-directed sedation (Elliott 2006), while non-randomized studies conducted in Europe identified mixed results. One Spanish study reported no difference in duration of mechanical ventilation (Arias-Rivera 2008), one Norwegian study reported a reduction in duration of mechanical ventilation and ICU length of stay (Brattebo 2002), two French studies involving adult participants identified a reduction in duration of mechanical ventilation (De Jonghe 2005; Quenot 2007), while a French study involving paediatric participants found no difference in duration of mechanical ventilation in the overall group but a reduction in ventilation in the subgroup aged > 12 years (Gaillard-Le Roux 2017). The only additional study conducted in North America was a retrospective chart review examining the effect of a pharmacist-developed sedation protocol, where a reduction in mechanical ventilation was identified but no details of the content of the protocol were provided (Hahn 2013). In one multicentre, two-phase study conducted in 13 ICUs in Chile, no change in ventilator-free days, mortality, ICU length of stay or post-traumatic stress symptoms 12 months later were identified (Bugedo 2013). These mixed results are likely to be influenced by multiple behavioural factors within the study sites, particularly the role of nurses in contributing to sedation management during usual care. One systematic review of observational and controlled studies examined multiple aspects of sedation practice to determine the impact of changes on economic and patient safety outcomes (Jackson 2010). When considering a broad methodological range of studies, the overall conclusion was that the introduction of guidelines and protocols generally improved outcomes. Furthermore, in one related systematic review of the effect of daily sedation interruption, there was no strong evidence of benefit from the intervention, although individual studies reported inconsistent results (Burry 2014). The reasons for these inconsistencies are likely to be multidimensional; however, they may include factors such as nurse:patient ratios, proportion of speciality specific postgraduate educated nurses, age of patients, sedative agents used during usual care and other related aspects, such as ventilation and mobilization practices. It is also possible

that the sedation protocols resulted in different practices of sedation administration that were not identified in the outcomes assessed in this review.

AUTHORS' CONCLUSIONS

Implications for practice

Currently, limited evidence from randomized controlled trials (RCTs) is available to evaluate the effectiveness of protocol-directed sedation on patient outcomes. The four included RCTs reported conflicting results in regard to some outcomes and heterogeneity limited the interpretation of results for many of the outcomes. While there was no evidence of a difference in harm between protocol-directed sedation and usual care, one non-randomized study reported an increase in intensive care unit (ICU) length of stay with the implementation of protocol-directed sedation (Elliott 2006). Consequently, the clinical context and practice roles of ICU clinicians should be considered prior to implementation of protocol-directed sedation management. In addition, there was general agreement that validated sedation assessment instruments should be used in all critical care settings and strategies to minimize sedation should be implemented (Barr 2013). The trend towards sedation minimization has been ongoing since the mid-2000s and is likely to continue, particularly in the context of related strategies to optimize early mobilization and reduce complications of intensive care such as delirium, and ongoing cognitive and psychological compromise (Needham 2012).

Implications for research

We do not have sufficient evidence to determine the effects of protocol-directed sedation on the outcomes of duration of mechanical ventilation, mortality and other related outcomes in adult and paediatric intensive care patients. Further research needs to be undertaken to ascertain the effect of protocol-directed sedation on patient outcomes. In particular, studies need to be conducted in a variety of clinical contexts to determine whether there are specific practice environments where benefit is more likely, as well as more studies being conducted within both the adult and paediatric settings as this might influence effectiveness. The issue of whether a study randomized at the level of the individual can be conducted without contamination needs to be considered; it may be that a cluster-randomized design, with multilevel statistical modelling, such as that used by Curley 2015, is required. Given there are multiple different strategies that have been developed in recent years to reduce the detrimental impact of sedation, the interaction between protocol-directed sedation and other sedation minimization strategies should also be examined. In the conduct of any studies undertaken to examine the impact of protocol-directed care, it is vital that a detailed description of both the experimental care process and usual care is provided. Furthermore, a range of both process and outcome measures should be incorporated into the design, with outcome measures extending beyond confines of ICU or the acute care hospital. Where relevant, outcomes that measure physical, cognitive and psychological health, as well as cost-effectiveness, should be incorporated (Needham 2012).

ACKNOWLEDGEMENTS

We would like to thank Jane Cracknell (Managing Editor, Cochrane Anaesthesia, Critical and Emergency Care (ACE)), and Karen Hovhannisyan (former Information Specialist, ACE) for their assistance in the preparation of the protocol (Aitken 2012), and previous review (Aitken 2015). We also thank Maria Isabel Castillo and Cesar Caramo for assistance with translating a Spanish language manuscript.

We would also like to thank Jane Cracknell (Managing Editor, Cochrane ACE), Janne Vendt (Cochrane Information Specialist), Harald Herkner (content and co-ordinating editor), Vibeke E Horstmann (statistical editor), and Marjolein de Wit, Lisa Burry (peer reviewers) and Anne Lyddiatt (consumer referee) for their help and editorial advice during the preparation of this updated Cochrane Review.

REFERENCES

References to studies included in this review

Brook 1999 *{published data only (unpublished sought but not used)}*

Brook AD, Ahrens TS, Schaiff R, Prentice D, Sherman G, Shannon W, et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Critical Care Medicine* 1999;**27**(12):2609-15. [PUBMED: 10628598]

Bucknall 2008 *{published and unpublished data}*

Bucknall TK, Manias E, Presneill JJ. A randomized trial of protocol-directed sedation management for mechanical ventilation in an Australian intensive care unit. *Critical Care Medicine* 2008;**36**(5):1444-50. [DOI: 10.1097/CCM.0b013e318168182d; PUBMED: 18434914]

Curley 2015 *{published and unpublished data}*

Curley MA, Wypij D, Watson S, Grant MJ, Asaro LA, Cheifetz IM, et al. RESTORE Study Investigators and the Pediatric Acute Lung Injury and Sepsis Investigators (PALIS) Network. Protocolized sedation vs usual care in pediatric patients mechanically ventilated for acute respiratory failure, a randomized clinical trial. *JAMA* 2015;**313**(4):379-89. [PUBMED: 25602358]

Mansouri 2013 *{published and unpublished data}*

Mansouri P, Javadpour S, Zand F, Ghodsbin F, Sabetian G, Masjedi M, et al. Implementation of a protocol for integrated management of pain, agitation, and delirium can improve clinical outcomes in the intensive care unit: a randomized clinical trial. *Journal of Critical Care* 2013;**28**(6):918-22. [PUBMED: 24011845]

References to studies excluded from this review

Arias-Rivera 2008 *{published data only}*

Arias-Rivera S, Sanchez-Sanchez MdM, Santos-Diaz R, Gallardo-Murillo J, Sanchez-Izquierdo R, Frutos-Vivar F, et al. Effect of a nursing-implemented sedation protocol on weaning outcome. *Critical Care Medicine* 2008;**36**(7):2054-60. [PUBMED: 18552689]

Brattebo 2002 *{published data only}*

Brattebo G, Hofoss D, Flaatten H, Muri AK, Gjerde S, Plsek PE. Effect of a scoring system and protocol for sedation on duration of patients' need for ventilator support in a surgical intensive care unit. *BMJ* 2002;**324**(7350):1386-9. [PUBMED: 12052813]

Bugedo 2013 *{published data only}*

Bugedo G, Tobar E, Aguirre M, Gonzalez H, Godoy J, Lira MT, L, et al. The implementation of an analgesia-based sedation protocol reduced deep sedation and proved to be safe and feasible in patients on mechanical ventilation [Implantacao de protocolo de reducao de sedacao profunda baseado em analgesia comprovadamente seguro e factivel em pacientes submetido a ventilaceo mecanica]. *Revista Brasileira de Terapia Intensiva* 2013;**25**(3):188-96. [DOI: 10.5935/0103-507X.20130034; PUBMED: 24213081]

De Jonghe 2005 *{published data only}*

De Jonghe B, Bastuji-Garin S, Fangio P, Lacherade J-C, Jabot J, Appere-De-Vecchi C, et al. Sedation algorithm in critically ill patients without acute brain injury. *Critical Care Medicine* 2005;**33**(1):120-7. [PUBMED: 15644658]

Elliott 2006 *{published data only}*

Elliott R, McKinley S, Aitken LM, Hendrikz J. The effect of an algorithm-based sedation guideline on the duration of mechanical ventilation in an Australian intensive care unit. *Intensive Care Medicine* 2006;**32**(10):1506-14. [PUBMED: 16896847]

Gaillard-Le Roux 2017 *{published data only}*

Gaillard-Le Roux B, Liet J-M, Bourgoin P, Legrand A, Roze J-C, Joram N. Implementation of a nurse-driven sedation protocol in a PICU decreases daily doses of midazolam. *Pediatric Critical Care Medicine* 2017;**18**(1):e9-e17. [DOI: 10.1097/PCC.0000000000000998; PUBMED: 27801707]

Hahn 2013 *{published data only}*

Hahn L, Beall J, Turner RS, Woolley TW, Hahn M. Pharmacist-developed sedation protocol and impact on ventilator days. *Journal of Pharmacy Practice* 2013;**26**(4):406-8. [DOI: 10.1177/0897190012467209; PUBMED: 23204145]

Quenot 2007 *{published data only}*

Quenot JP, Ladoire S, Devoucoux F, Doise JM, Cailliod R, Cunin N, et al. Effect of a nurse-implemented sedation protocol on the incidence of ventilator-associated pneumonia. *Critical Care Medicine* 2007;**35**(9):2031-6. [PUBMED: 17855817]

Tobar 2008 *{published and unpublished data}*

Tobar AE, Lanas MA, Pino PS, Aspee LP, Rivas VS, Prat RD, et al. Protocol based sedation versus conventional treatment in critically ill patients on mechanical ventilation [Sedacion guiada por protocolo versus manejo convencional en pacientes criticos en ventilacion mecanica]. *Revista Médica de Chile* 2008;**136**(6):711-8. [PUBMED: 18769826]

Additional references

Barr 2013

Barr J, Fraser GL, Puntillo K, Ely EW, Gelinas C, Dasta JF, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Critical Care Medicine* 2013;**41**(1):263-306. [PUBMED: 23269131]

Blackwood 2014

Blackwood B, Burns KEA, Cardwell CR, O'Halloran P. Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients. *Cochrane Database of Systematic Reviews* 2014, Issue 11. [DOI: 10.1002/14651858.CD006904.pub3]

Burry 2014

Burry L, Rose L, McCullagh IJ, Fergusson DA, Ferguson ND, Mehta S. Daily sedation interruption versus no daily sedation interruption for critically ill adult patients requiring invasive mechanical ventilation. *Cochrane Database of Systematic Reviews* 2014, Issue 7. [DOI: 10.1002/14651858.CD009176.pub2]

Curley 2006

Curley MA, Harris SK, Fraser KA, Johnson RA, Arnold JH. State Behavioral Scale: a sedation assessment instrument for infants and young children supported on mechanical ventilation. *Pediatric Critical Care Medicine* 2006;**7**(2):107-14. [PUBMED: 16446601]

Elliott 2013

Elliott D, Aitken LM, Bucknall TK, Seppelt IM, Webb SA, Weisbrodt L, et al. Patient comfort in the intensive care unit: a multicentre, binational point prevalence study of analgesia, sedation and delirium management. *Critical Care and Resuscitation* 2013;**15**(3):213-9. [PUBMED: 23944208]

Ely 2003

Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA* 2003;**289**(22):2983-91. [PUBMED: 12799407]

Girard 2008

Girard TD, Pandharipande PP, Ely EW. Delirium in the intensive care unit. *Critical Care* 2008;**12 Suppl 3**:3. [PUBMED: 18495054]

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro GDT. Version accessed 16 September 2016. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Guyatt 2008

Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians. *BMJ* 2008;**336**(7651):995-8. [PUBMED: 18456631]

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Jackson 2009

Jackson DL, Proudfoot CW, Cann KF, Walsh TS. The incidence of sub-optimal sedation in the ICU: a systematic review. *Critical Care* 2009;**13**(6):R204. [PUBMED: 20015357]

Jackson 2010

Jackson DL, Proudfoot CW, Cann KF, Walsh T. A systematic review of the impact of sedation practice in the ICU on resource use, costs and patient safety. *Critical Care* 2010;**14**(2):R59. [PUBMED: 20380720]

Jacobi 2002

Jacobi J, Fraser GL, Coursin DB, Riker RR, Fontaine D, Wittbrodt ET, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Critical Care Medicine* 2002;**30**(1):119-41. [PUBMED: 11902253]

Kollef 1998

Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G. The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation. *Chest* 1998;**114**(2):541-8. [PUBMED: 9726743]

Kress 2000

Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *New England Journal of Medicine* 2000;**342**(20):1471-7. [PUBMED: 10816184]

Mehta 2009

Mehta S, McCullagh I, Burry L. Current sedation practices: lessons learned from international surveys. *Critical Care Clinics* 2009;**25**(3):471-88. [PUBMED: 19576525]

Moher 2009

Moher D, Liberati A, Tetzlaff J, ALtman DG, The PRISMA group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.. *PLoS Med* 2009;**6**(7):e1000097. [PUBMED: 19621072]

Needham 2012

Needham DM, Davidson J, Cohen H, Hopkins RO, Weiner C, Wunsch H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Critical Care Medicine* 2012;**40**(2):502-9. [DOI: 10.1097/CCM.0b013e318232da75]

O'Connor 2009

O'Connor M, Bucknall T, Manias E. Sedation management in Australian and New Zealand intensive care units: doctors' and nurses' practices and opinions. *American Journal of Critical Care* 2009;**19**(3):285-95. [PUBMED: 19770414]

Rao 1992

Rao JN, Scot AJ. A simple method for the analysis of clustered binary data. *Biometrics* 1992;**48**:577-85.

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Richards-Belle 2016

Richards-Belle A, Canter RR, Power GS, Robinson EJ, Reschreiter H, Wunsch H, et al. National survey and point prevalence study of sedation practice in UK critical care. *Critical Care* 2016;**20**(1):355. [DOI: 10.1186/213054-016-1532-x; PUBMED: 27788680]

Riker 1999

Riker RR, Picard JT, Fraser GL. Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. *Critical Care Medicine* 1999;**27**(7):1325-9. [PUBMED: 10446827]

Ringdal 2006

Ringdal M, Johansson L, Lundberg D, Bergbom I. Delusional memories from the intensive care unit experienced by patients with physical trauma. *Intensive and Critical Care Nursing* 2006;**22**(6):346-54. [PUBMED: 16901701]

Samuelson 2006

Samuelson K, Lundberg D, Fridlund B. Memory in relation to depth of sedation in adult mechanically ventilated intensive care patients. *Intensive Care Medicine* 2006;**32**(5):660-7. [PUBMED: 16520999]

Schweickert 2008

Schweickert WD, Kress JP. Strategies to optimize analgesia and sedation. *Critical Care* 2008;**12 Suppl 3**:6. [PUBMED: 18495057]

Sessler 2009

Sessler CN, Pedram S. Protocolized and target-based sedation and analgesia in the ICU. *Critical Care Clinics* 2009;**25**(3):489-513. [PUBMED: 19576526]

Shehabi 2013

Shehabi Y, Chan L, Kadiman S, Alias A, Ismail WN, Tan MA, et al. The Sedation Practice in Intensive Care Evaluation (SPICE) Study Group Investigators. Sedation depth and long-term mortality in mechanically ventilated critically ill adults: a prospective longitudinal multicentre cohort study. *Intensive Care Medicine* 2013;**39**(5):910-8. [DOI: 10.1007/s00134-013-2830-2; PUBMED: 23344834]

Walsh 2016

Walsh TS, Kydonaki K, Antonelli J, Stephen J, Lee RJ, Everingham K, et al. Development and Evaluation of Strategies to Improve Sedation Practice Intensive Care (DESIST) study investigators. Staff education, regular sedation and analgesia quality feedback, and a sedation monitoring technology for improving sedation and analgesia quality for critically ill, mechanically ventilated patients: a cluster randomised trial. *Lancet. Respiratory Medicine* 2016;**4**(10):807-17. [DOI: 10.1016/S2213-2600(16)30178-3; PUBMED: 27473760]

References to other published versions of this review

Aitken 2012

Aitken LM, Bucknall T, Kent B, Michell M, Burmeister E, Keogh SJ. Protocol-directed sedation versus non-protocol-directed sedation to reduce duration of mechanical ventilation in mechanically ventilated intensive care patients. *Cochrane Database of Systematic Reviews* 2012, Issue 4. [DOI: 10.1002/14651858.CD009771]

Aitken 2015

Aitken LM, Bucknall T, Kent B, Mitchell M, Burmeister E, Keogh SJ. Protocol-directed sedation versus non-protocol-directed sedation to reduce duration of mechanical ventilation in mechanically ventilated intensive care patients. *Cochrane Database of Systematic Reviews* 2015, Issue 1. [DOI: 10.1002/14651858.CD009771.pub2]

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Brook 1999

Methods	Randomized, controlled clinical trial
Participants	**Setting**: study conducted from August 1997 to July 1998 in university-affiliated urban teaching hospital in USA; closed medical ICU (19 beds); nurse:patient ratio of 2:1 to 3:1 **Participants**: 332 participants requiring mechanical ventilation were randomized; 4 participants were randomized twice (their second study admission was excluded) and 7 surgical patients were awaiting transfer to the surgical ICU (and therefore met the exclusion criteria). 321 participants were included in the analysis **Participant characteristics**: mean age: 58 years in both groups; gender: 51% men (protocol group), 47% men (usual care group); APACHE II score: 23 in both groups; common diagnoses: pneumonia (21% protocol group, 30% usual care group), COPD or asthma (17% protocol group, 15% usual care group), sepsis (17% protocol group, 15% usual care group)
Interventions	Protocol-directed sedation versus non-protocol-directed sedation (usual care). Sedation protocol required nurses to determine whether analgesics (morphine, fentanyl), sedatives (diazepam, midazolam, lorazepam), or both were needed to provide optimal patient care. The type of sedation administration (i.e. bolus versus continuous) as well as the dosage were determined by the nursing staff with reference to the Ramsay Scale. Weaning or withdrawal from sedation was also guided by protocol. Treating physicians could deviate patient management from the protocol, including using non-protocol seda-

Brook 1999 *(Continued)*

	tives. Non-protocol-directed sedation was ordered by the treating physician; nurses were only able to make changes with a physician's written or verbal order
Outcomes	**Primary outcome** 1. Duration of mechanical ventilation **Secondary outcomes included** 1. ICU and hospital lengths of stay 2. Hospital mortality 3. Rates of development of organ system derangements 4. Reintubation 5. Tracheostomy
Notes	**Funding:** supported, in part, by the Barnes-Jewish Hospital Innovations in Healthcare Program

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Blocked randomization was used, but no detail was provided regarding how the randomization sequence was generated
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes that were opened each time a participant was enrolled; unclear if envelopes were sequentially numbered
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel was undertaken, this would have been difficult to achieve, but may have influenced processes of care. Performance bias (personnel) was unclear, as treating physicians were able to deviate from the protocol, and physicians in the physician-directed control group could alter their practices as desired
Blinding of outcome assessment (detection bias) All outcomes	Low risk	There was no blinding of outcome assessors; however, given all outcomes were objectively measured, the risk of biasing results was low
Incomplete outcome data (attrition bias) All outcomes	Low risk	11 participants were randomized but not included in the analysis: 4 were randomized twice (the second randomization was excluded) and 7 were randomized while they were waiting for transfer to the surgical ICU (and therefore met exclusion criteria). Intention-to-treat analysis was conducted on a sample of 321 participants. Incomplete data from 106 participants who died and were not successfully weaned from mechanical ventilation - data from these participants were labelled as censored data. Censored data were included in all univariate analysis (primary and secondary outcomes) with removal of censored data from prespecified posthoc analysis
Selective reporting (reporting bias)	Unclear risk	No registration of study or publication of study protocol; however, all primary and secondary outcomes results and prespecified analyses were reported according to the aims stated in the publication
Other bias	Unclear risk	Usual care was not described, except for the number of participants and duration of chemical paralysis. Unclear if standard management practices (mode of mechanical ventilation, physiotherapy, suctioning, repositioning, investigations outside ICU, need for physical restraints) or nurse:patient ratios were equally applied to both groups. If standard management practices differed between groups, there was a risk of bias.

Brook 1999 *(Continued)*

	Baseline participant characteristics were described as similar between groups, with variables of interest tabulated in the report and no statistically significant differences found, including the indication for mechanical ventilation and severity of illness scores (APACHE II, predicted mortality). However, the control group had a higher trend for the number of participants with pneumonia (34 participants in the protocol group versus 47 participants in the usual care group, P = 0.077). Potential for contamination between the 2 groups existed as participants were cared for in the same ICU at the same time and care of usual care group participants was directed by individual physician preferences, so the principles of protocol-directed care may have been partially applied to the control group

Bucknall 2008

Methods	Randomized controlled trial
Participants	**Setting**: study conducted September 2001 to April 2002 in a metropolitan teaching hospital in Australia; closed general ICU (24 beds); nurse:patient ratio 1:1 **Participants**: 316 mechanically ventilated ICU participants were randomized in the study. 4 participants were excluded from final analysis due to inappropriate re-enrolment into the study following readmission to ICU. 312 participants were included in the final analysis **Participants characteristics**: mean age: 58 years in protocol group, 56 years in usual care group; gender: 64% men (protocol group), 58% men (usual care group); APACHE II score: 19 in protocol group, 20 in usual care group; diagnostic groups: medical (69% protocol group, 59% usual care group), surgical (12% protocol group, 17% usual care group), trauma (19% protocol group, 24% usual care group)
Interventions	Protocol-directed sedation versus non-protocol-directed sedation. Within the protocol-directed sedation group, physicians prescribed the medications contained within the protocol. Nurses determined the type and dosage of sedation (midazolam, propofol) or analgesia (morphine) (or both) and the method of administration (infusion or intermittent dose). Sedation was guided by assessment using the Sedation-Agitation Scale. The protocol was sufficiently flexible to allow the de-escalation of sedation dose every 2 hours to avoid over-sedation. Non-protocol sedation type and dose limits for both infusion and boluses were prescribed by ICU medical staff with nurses able to assess, titrate and manage within those orders, including complete cessation of sedation. Nurses could communicate with any member of the ICU medical team if they believed changes to the written sedation orders were needed
Outcomes	**Primary outcome** 1. Tme from commencement of mechanical ventilation in the ICU to successful weaning from mechanical ventilation **Secondary outcomes** 1. Duration of ICU and hospital length of stay 2. ICU and hospital mortality 3. Rates of self-extubation 4. Rates of tracheostomy
Notes	**Funding**: in part through an Abbott Australasia Research Grant and the Australian College of Critical Care Nurses - these bodies did not influence the study design, implementation, analysis or conclusions

Risk of bias

Bias	Authors' judgement	Support for judgement

Bucknall 2008 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomization using a simple 1:1 randomization sequence. Randomization sequence was computer generated
Allocation concealment (selection bias)	Low risk	Participants were randomized to protocol or non-protocol sedation by the senior nurse on duty, who chose the next serially numbered sealed opaque envelope
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were not blinded, this would have been difficult to achieve given the nature of the intervention, but may have influenced processes of care. All ICU nurses were required to attend an education session on the implementation of the study and the sedation protocol. No comment regarding deviation from the protocol by medical staff was provided, although non-protocol drugs were administered to participants in the protocol group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	ICU research nurses collected outcomes data; no information was provided as to whether they were blinded to group allocation. However, given the objective nature of the outcomes (duration of mechanical ventilation, ICU and hospital length of stay, mortality, self-extubation, tracheostomy rates), the potential for this knowledge to bias outcome measurement was low
Incomplete outcome data (attrition bias) All outcomes	Low risk	316 participants were enrolled and randomized in the study, 4 participants were excluded from analysis due to inappropriate re-enrolment during a readmission to ICU. Outcome data were provided for the remaining 312 participants and included in final analysis
Selective reporting (reporting bias)	Low risk	No registration on study or publication of study protocol; however, all primary and secondary outcomes and all prespecified analyses were reported according to the aims stated in the publication
Other bias	Unclear risk	A description of usual care for general management and specific sedation management was provided, although some associated aspects of care such as physiotherapy, suctioning, repositioning, investigations outside ICU and need for physical restraints were not provided. If standard management practices differed between groups, there was a risk of bias. Baseline participant characteristics (age, gender, diagnosis, APACHE II score, SAPS II score) were described as similar between groups. Potential for contamination between the 2 groups existed as participants were cared for in the same ICU at the same time and care of control group participants was directed by ICU medical staff in line with usual local practice. It is possible that the principles of protocol-directed care could have been partially applied to the control group

Curley 2015

Methods	Cluster-randomized controlled trial
Participants	**Setting:** study conducted from June 2009 to December 2013 in 31 different paediatric intensive care units across USA, 90% university-affiliated; 20 units open; nurse:patient ratio 1:1 for an average of 30% of staffing **Participants:** 2449 children were enrolled with 1225 in intervention sites and 1224 in control sites; 25 children were withdrawn from the protocol in intervention sites, however all enrolled children were included in the analysis **Participant characteristics:** median age 1.4 (0.3 - 7.0) years in protocol group and 2.6 (0.6 - 9.2) years in usual care group, P = 0.002; 46% female in protocol group and 44% female in usual care group;

Curley 2015 *(Continued)*

	PRISM III-12 score: median 6 (3 - 11) in protocol group and 8 (5 - 13.5) in usual care group, P = 0.005; diagnostic groups: pneumonia - 32% protocol, 35% usual care; bronchiolitis - 35% protocol, 19% usual care; acute respiratory failure related to sepsis - 12% protocol, 17% usual care; asthma or reactive airway disease - 7% protocol, 10% usual care; aspiration pneumonia - 6% protocol, 6% usual care; other - 8% protocol, 12% usual care; P < 0.001
Interventions	Protocol-directed sedation versus non-protocol-directed sedation. The sedation protocol incorporated interprofessional team training and use of a nurse-implemented, goal-directed comfort algorithm to guide sedation therapy. Core elements of the protocol included daily team discussion of the patient's trajectory of illness, prescription of a State Behavioural Scale (SBS) target score, arousal assessment, daily extubation readiness test when appropriate, adjustment of sedatives at least every 8 hours, discontinuation of opioids and benzodiazepines when no longer necessary and a written sedation weaning plan when transferred out of the ICU. Primary sedative agents included morphine and midazolam. Fentanyl was recommended as a primary agent for participants with hypotension or reactive airways disease. Non-protocol-directed sedation was managed without a protocol and sedatives were selected, prescribed and titrated at the discretion of the medical team, no recommendations were made for extubation readiness testing
Outcomes	**Primary outcome** 1. Duration of mechanical ventilation **Secondary outcomes** 1. Time to recovery from acute respiratory failure 2. Duration of weaning from mechanical ventilation 3. Neurological testing 4. Intensive care length of stay 5. Hospital length of stay 6. In-hospital mortality 7. Sedation-related adverse events 8. Sedative exposure 9. Occurrence of iatrogenic withdrawal
Notes	Clinicaltrials.gov Identifier: NCT00814099 **Funding:** National Heart, Lung and Blood Institute and the National Institute of Nursing Research, National Institutes of Health

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated clusters (hospitals) were randomized within strata (according to PICU size) and assigned via computer-generated random numbers. More PICUs were randomized to the intervention group than the control group due to anticipated lower consent rates, but how this was achieved is not described
Allocation concealment (selection bias)	High risk	Centres were provided with a copy of the protocol that described the intervention in general terms and were allocated after baseline data were collected, but no information regarding this process was provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants and personnel were not blinded; this would have been difficult to achieve given the nature of the intervention. Given entire clusters (hospitals) were allocated to either control or intervention, and therefore processes became standard of care in each centre, the risk of performance bias is unclear. Adherence to elements of the sedation protocol were measured and reported

Curley 2015 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	It is not clear who collected outcomes data, although given the unblinded nature of the study they would not have been blinded to group allocation. Given the objective nature of the outcomes (duration of mechanical ventilation, time to recovery from acute respiratory failure, duration of weaning from mechanical ventilation, neurological testing, PICU and hospital length of stay, in-hospital mortality, sedation-related adverse events, sedative exposure and occurrence of iatrogenic withdrawal), the potential for this knowledge to bias outcome was low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data for 10 participants in the intervention group were not available due to withdrawal of consent for all aspects of the study; otherwise data collection is complete
Selective reporting (reporting bias)	Low risk	All outcomes (primary and secondary) were selected a priori and have been addressed in this report and associated supplemental information. The study protocol was registered on ClinicalTrials.gov prior to study commencement
Other bias	Low risk	Extensive reporting of sedation and pain assessment and management practices in both groups, with no evidence of contamination between the two groups

Mansouri 2013

Methods	Randomized controlled trial
Participants	**Setting**: study conducted in 2011 in a university hospital in Iran with 2 mixed ICUs **Participants**: 216 mixed medical-surgical ICU patients were enrolled, 15 participants were excluded from the protocol group because of violation of the protocol. Analysis incorporated 201 participants (96 - protocol, 105 - control) **Participant characteristics**: age - 53 ± 20 years; male gender - 64% protocol, 63% control; APACHE IV mean (SD) - 86 (30) protocol, 75 (33) control, postoperative admission - 77% protocol, 65% control
Interventions	Protocol-directed management of pain, agitation and delirium versus usual care. Protocol-directed management was designed to keep the BPS less than 5, the NRS less than 3 and the RASS between -1 and +1 following a first-analgesia policy. Assessment incorporated evaluation using the BPS or NRS and the RASS every hour, the CAM-ICU every working shift and whenever deemed needed. Daily sedation interruptions were not included. The nurses had the authority to adjust the analgesic and sedative drugs according to the protocol to keep the pain and agitation scores within the acceptable range. If delirium was positive, the participants were treated according to the protocol. Usual care involved pain and sedation being managed as routine according to as-needed physician orders without regular assessment for pain, sedation or delirium
Outcomes	**Outcomes** 1. Length of ICU stay (hours) 2. Duration of mechanical ventilation (hours) 3. ICU mortality 4. Self-extubations 5. Effectiveness of the protocol to control pain 6. Agitation and delirium 7. Dose of drugs used to treat pain 8. Agitation 9. Delirium

Mansouri 2013 *(Continued)*

Notes	Nurses in the study ICUs were encouraged to participate in the project by both financial and non-financial incentives (no further details provided) **Funding**: Shiraz University of Medical Sciences

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly assigned to the protocol or the control group based on a computer-generated table of random numbers.
Allocation concealment (selection bias)	Unclear risk	No information is provided regarding how the group allocation process was conducted.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were not blinded; this would have been difficult to achieve given the nature of the intervention, but may have influenced processes of care. ICU nurses were required to attend education sessions and the knowledge and skill of the nurses on the pain, agitation and delirium scores and use of the study protocol was tested twice (once during the first month and again during the fourth month of the study). Adherence to the protocol was monitored by 1 researcher and 2 assistants on all shifts with 15 participants excluded from the protocol group because of violation of the protocol by the nurses.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	It is not clear who collected outcomes data, although given the unblinded nature of the study they were unlikely to have been blinded to group allocation. Given the objective nature of most of the outcomes (ICU length of stay, duration of mechanical ventilation, all-cause mortality in ICU, self-extubations), the risk of bias was assessed as low.
Incomplete outcome data (attrition bias) All outcomes	High risk	216 participants enrolled in the study (111 protocol group; 105 control group); 15 participants were excluded from the protocol group due to protocol violations with 201 participants included in analysis (96 protocol group; 105 control group). Intention-to-treat analysis not used
Selective reporting (reporting bias)	Unclear risk	No registration on study or publication of study protocol; however, all primary and secondary outcomes were reported according to the aims stated in the publication. The effectiveness of control of pain, agitation and delirium was only able to be assessed in the protocol group as these parameters were not assessed in the control group.
Other bias	Unclear risk	Limited description of usual care has been provided, with information about what was not done (e.g. assessment of pain, agitation and delirium) provided. A description of associated aspects of care, such as physiotherapy, suctioning, repositioning, investigations outside ICU and need for physical restraints were not provided. If standard management practices differed between groups, there was a risk of bias. Limited baseline participant characteristics (age, gender, APACHE IV score, postoperative admission) were described as similar between groups. Potential for contamination between the 2 groups existed as participants were cared for in the same ICU at the same time. It is possible that some of the principles of protocol-directed care could have been partially applied to the control group

Acronyms and abbreviations:

APACHE: Acute Physiology and Chronic Health Evaluation; BPS: Behavioural Pain Scale; CAM: Confusion Assessment Method; COPD: chronic obstructive pulmonary disease; ICU: intensive care unit; NRS: Numeric Rating Scale; PICU: paediatric intensive care unit; PRISM: Pediatric Risk of Mortality; RASS: Richmond Agitation Sedation Scale; SAPS: Simplified Acute Physiology Score; SBS: State Behavioral Scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arias-Rivera 2008	Not a RCT; was a before-and-after prospective study of the effect of introducing nurse-directed sedation
Brattebo 2002	Not a RCT; was a pre-intervention, postintervention observational study of the effect of introducing protocol-directed sedation
Bugedo 2013	Not a RCT; was a 2-phase prospective non-randomized multicentre study of the effect of an analgesia-based, goal-directed nurse-driven sedation protocol
De Jonghe 2005	Not a RCT; was a 2-phase prospective controlled study examining the effect of protocol-directed sedation
Elliott 2006	Not a RCT' was a pre-intervention, postintervention comparative investigation of the effect of protocol-directed sedation
Gaillard-Le Roux 2017	Not a RCT; was a prospective before-and-after study of the impact of a nurse-driven sedation protocol
Hahn 2013	Not a RCT; was a retrospective chart review of participants cared for prior to, and after, implementation of a sedation protocol
Quenot 2007	Not a RCT; was a 2-phase (before-and-after) prospective controlled study examining the effect of protocol-directed sedation
Tobar 2008	Did not measure outcomes of interest; was an RCT examining the effect of protocol-directed sedation on proportion of patient assessments in desired sedation range as well as amount of sedative agents used

RCT: randomized controlled trial

DATA AND ANALYSES

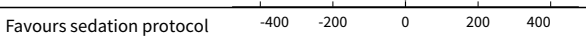
Comparison 1. Protocol-directed sedation management compared with usual care

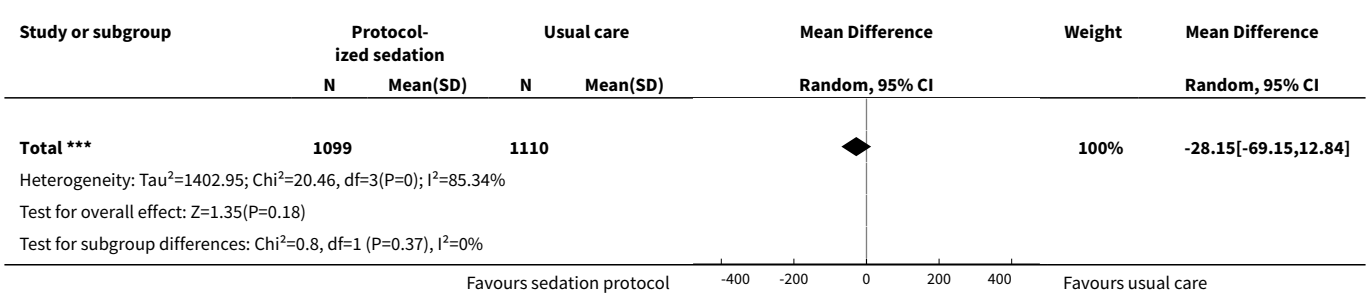
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of mechanical ventilation	4	2209	Mean Difference (IV, Random, 95% CI)	-28.15 [-69.15, 12.84]
1.1 Adult patients	3	834	Mean Difference (IV, Random, 95% CI)	-41.44 [-111.07, 28.19]
1.2 Paediatric patients	1	1375	Mean Difference (IV, Random, 95% CI)	-8.40 [-28.15, 11.35]
2 ICU mortality	2	513	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.39, 1.50]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Hospital mortality	3	2008	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.72, 1.13]
3.1 Adult patients	2	633	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.71, 1.31]
3.2 Paediatric patients	1	1375	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.51, 1.17]
4 ICU length of stay	4	2123	Mean Difference (IV, Random, 95% CI)	-1.70 [-3.71, 0.31]
4.1 Adult patients	3	834	Mean Difference (IV, Random, 95% CI)	-2.21 [-5.25, 0.83]
4.2 Paediatric patients	1	1289	Mean Difference (IV, Random, 95% CI)	-0.80 [-2.25, 0.65]
5 Hospital length of stay	3	1922	Mean Difference (IV, Random, 95% CI)	-3.09 [-5.08, -1.10]
5.1 Adult patients	2	633	Mean Difference (IV, Random, 95% CI)	-3.78 [-8.54, 0.97]
5.2 Paediatric patients	1	1289	Mean Difference (IV, Random, 95% CI)	-2.70 [-5.02, -0.38]
6 Self-extubation	2	1687	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.55, 1.42]
7 Reintubation	1	321	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.35, 1.24]
8 Incidence of tracheostomy	3	2008	Risk Ratio (IV, Random, 95% CI)	0.67 [0.35, 1.30]
8.1 Adult patients	2	633	Risk Ratio (IV, Random, 95% CI)	0.77 [0.31, 1.89]
8.2 Paediatric patients	1	1375	Risk Ratio (IV, Random, 95% CI)	0.47 [0.22, 1.04]

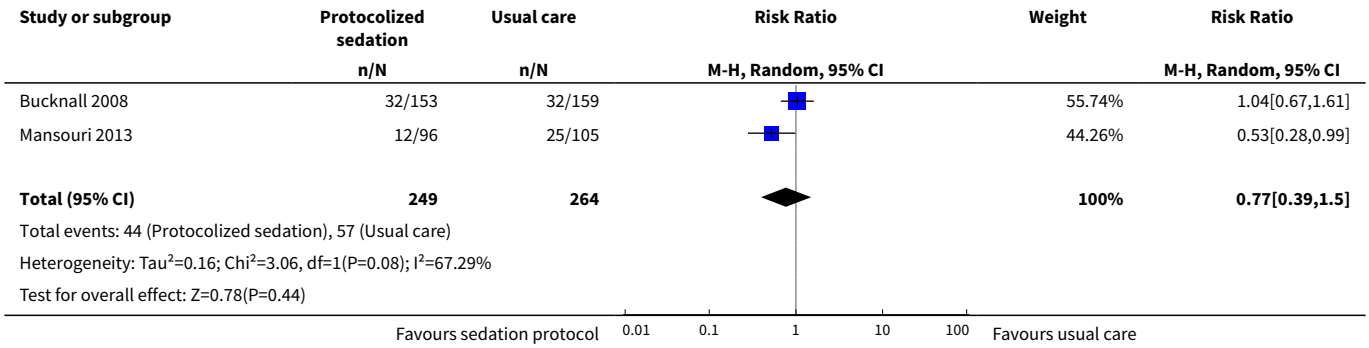
Analysis 1.1. Comparison 1 Protocol-directed sedation management compared with usual care, Outcome 1 Duration of mechanical ventilation.

Study or subgroup	Protocol-ized sedation N	Protocol-ized sedation Mean(SD)	Usual care N	Usual care Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.1.1 Adult patients							
Brook 1999	162	89.1 (133.6)	159	124 (153.6)		26.33%	-34.9[-66.42,-3.38]
Bucknall 2008	153	115.9 (146.6)	159	93.4 (103.2)		27.16%	22.53[-5.7,50.76]
Mansouri 2013	96	63.1 (112.4)	105	193 (320)		17.43%	-129.9[-195.11,-64.69]
Subtotal ***	**411**		**423**			**70.92%**	**-41.44[-111.07,28.19]**
Heterogeneity: Tau^2=3303.43; Chi^2=20.25, df=2(P<0.0001); I^2=90.12%							
Test for overall effect: Z=1.17(P=0.24)							
1.1.2 Paediatric patients							
Curley 2015	688	219.3 (178.2)	687	227.7 (195)		29.08%	-8.4[-28.15,11.35]
Subtotal ***	**688**		**687**			**29.08%**	**-8.4[-28.15,11.35]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.83(P=0.4)							

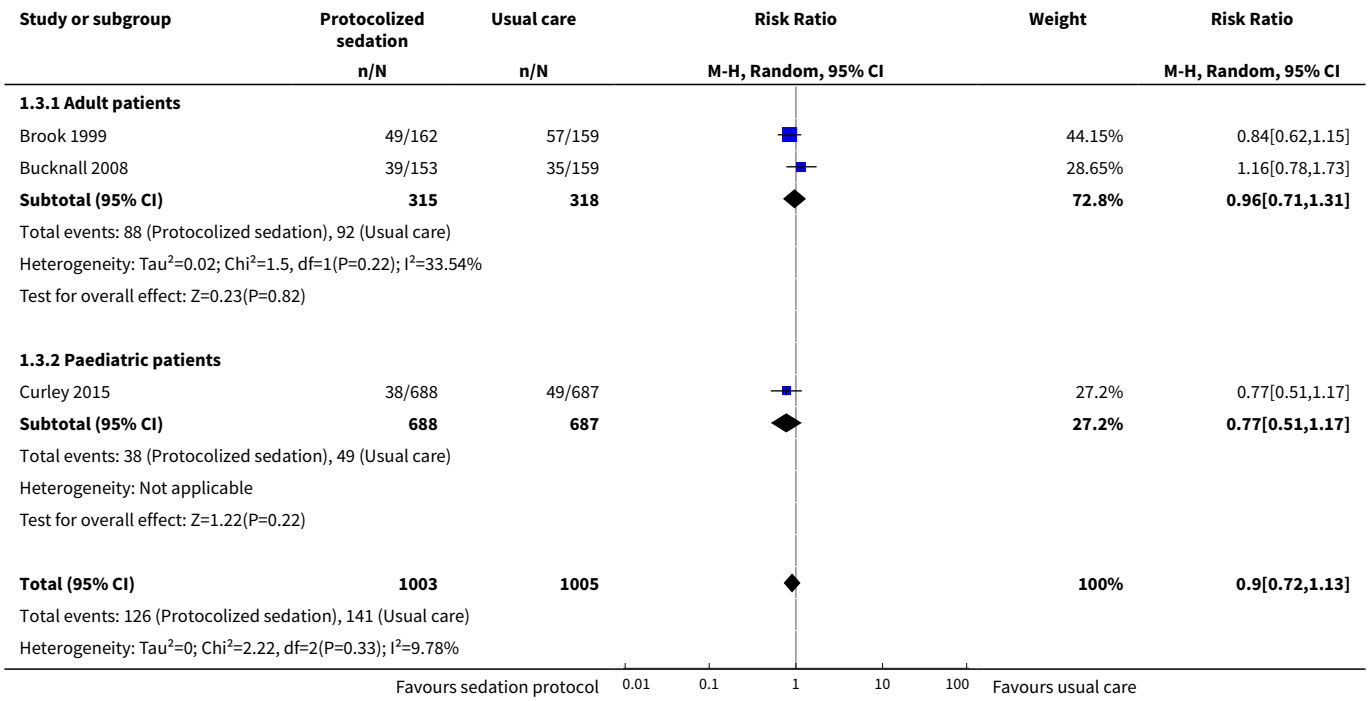




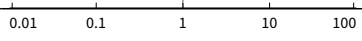
Analysis 1.2. Comparison 1 Protocol-directed sedation management compared with usual care, Outcome 2 ICU mortality.



Analysis 1.3. Comparison 1 Protocol-directed sedation management compared with usual care, Outcome 3 Hospital mortality.



Study or subgroup	Protocolized sedation	Usual care	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Test for overall effect: Z=0.9(P=0.37)					
Test for subgroup differences: Chi²=0.7, df=1 (P=0.4), I²=0%					



Favours sedation protocol — Favours usual care

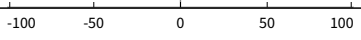
Analysis 1.4. Comparison 1 Protocol-directed sedation management compared with usual care, Outcome 4 ICU length of stay.

Study or subgroup	Protocol-ized sedation		Usual care		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
1.4.1 Adult patients							
Brook 1999	162	5.7 (5.9)	159	7.5 (6.5)		27.77%	-1.8[-3.16,-0.44]
Bucknall 2008	153	6.6 (7.2)	159	6 (6.2)		27.06%	0.6[-0.89,2.09]
Mansouri 2013	96	6.6 (7.8)	105	13 (14.3)		17.89%	-6.4[-9.55,-3.25]
Subtotal ***	**411**		**423**			**72.71%**	**-2.21[-5.25,0.83]**
Heterogeneity: Tau²=6.13; Chi²=16.8, df=2(P=0); I²=88.09%							
Test for overall effect: Z=1.42(P=0.15)							
1.4.2 Paediatric patients							
Curley 2015	651	13.2 (12.5)	638	14 (14)		27.29%	-0.8[-2.25,0.65]
Subtotal ***	**651**		**638**			**27.29%**	**-0.8[-2.25,0.65]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.08(P=0.28)							
Total ***	**1062**		**1061**			**100%**	**-1.7[-3.71,0.31]**
Heterogeneity: Tau²=3.32; Chi²=17.04, df=3(P=0); I²=82.4%							
Test for overall effect: Z=1.65(P=0.1)							
Test for subgroup differences: Chi²=0.67, df=1 (P=0.41), I²=0%							

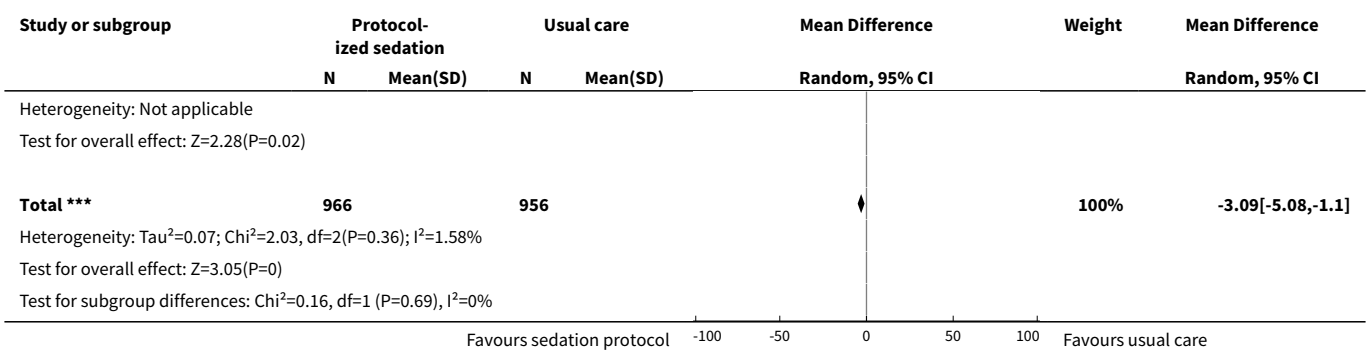
Favours sedation protocol — Favours usual care

Analysis 1.5. Comparison 1 Protocol-directed sedation management compared with usual care, Outcome 5 Hospital length of stay.

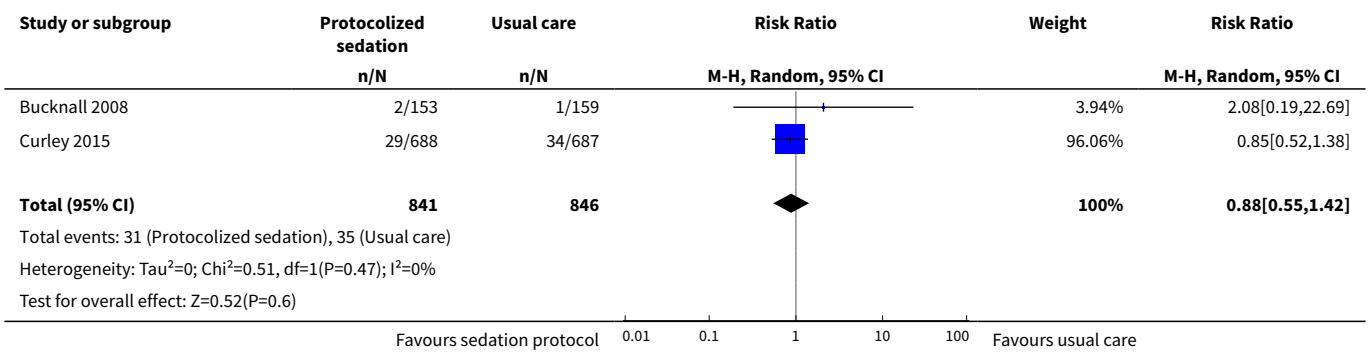
Study or subgroup	Protocol-ized sedation		Usual care		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
1.5.1 Adult patients							
Brook 1999	162	14 (17.3)	159	19.9 (24.2)		18.37%	-5.9[-10.51,-1.29]
Bucknall 2008	153	18.2 (19.2)	159	19.2 (31.9)		11.59%	-1[-6.82,4.82]
Subtotal ***	**315**		**318**			**29.96%**	**-3.78[-8.54,0.97]**
Heterogeneity: Tau²=4.83; Chi²=1.67, df=1(P=0.2); I²=40.27%							
Test for overall effect: Z=1.56(P=0.12)							
1.5.2 Paediatric patients							
Curley 2015	651	20.7 (19.5)	638	23.4 (22.8)		70.04%	-2.7[-5.02,-0.38]
Subtotal ***	**651**		**638**			**70.04%**	**-2.7[-5.02,-0.38]**



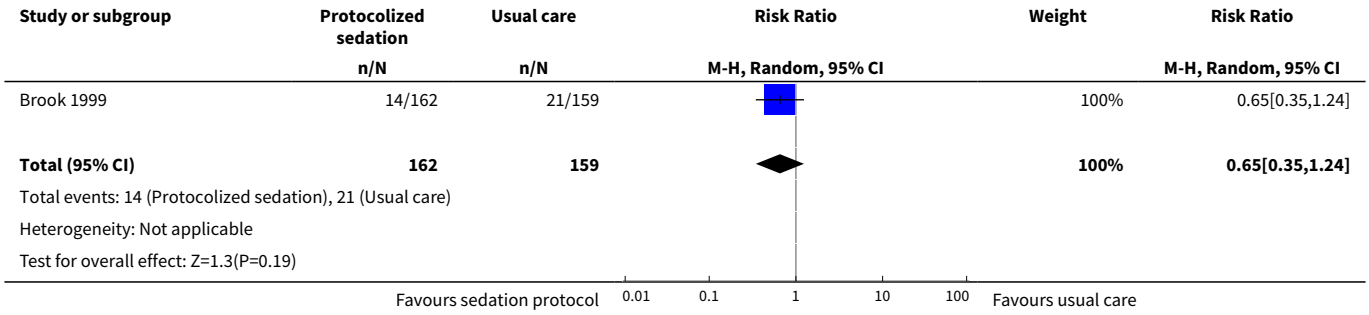
Favours sedation protocol — Favours usual care



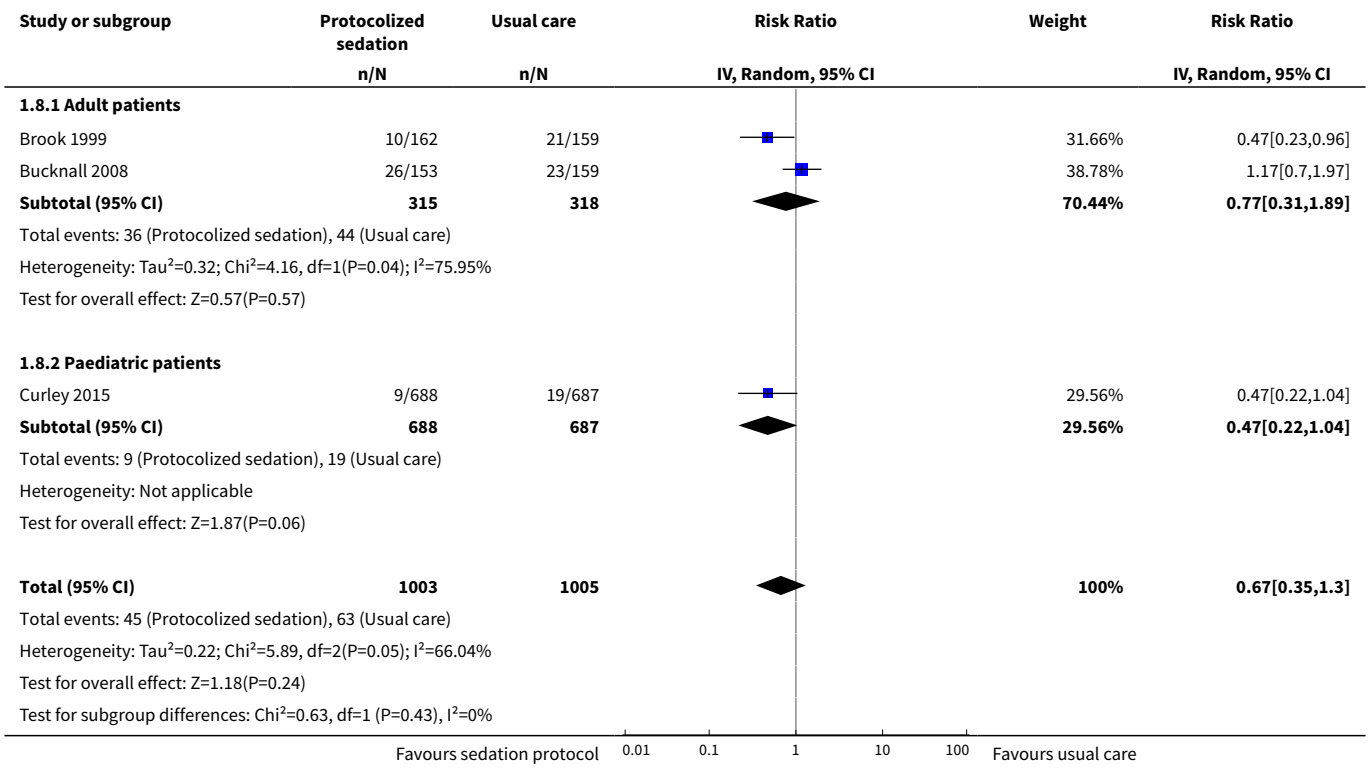
Analysis 1.6. Comparison 1 Protocol-directed sedation management compared with usual care, Outcome 6 Self-extubation.



Analysis 1.7. Comparison 1 Protocol-directed sedation management compared with usual care, Outcome 7 Reintubation.



Analysis 1.8. Comparison 1 Protocol-directed sedation management compared with usual care, Outcome 8 Incidence of tracheostomy.



APPENDICES

Appendix 1. Search strategies

CENTRAL search strategy

#1 MeSH descriptor: [Algorithms] explode all trees

#2 MeSH descriptor: [Guidelines as Topic] explode all trees

#3 MeSH descriptor: [Clinical Protocols] explode all trees

#4 MeSH descriptor: [Medication Therapy Management] explode all trees

#5 (protocol* or non?protocol* or directed or guide* or algorithm* or manage* or ((standar* or regular*) near assess*)):ti,ab

#6 (#1 or #2 or #3 or #4 or #5)

#7 MeSH descriptor: [Conscious Sedation] explode all trees

#8 MeSH descriptor: [Analgesia, Patient-Controlled] explode all trees

#9 MeSH descriptor: [Analgesics] explode all trees

#10 MeSH descriptor: [Hypnotics and Sedatives] explode all trees

#11 (sedat* or analge*):ti,ab

#12 (#7 or #8 or #9 or #10 or #11)

#13 MeSH descriptor: [Critical Care] explode all trees

#14 MeSH descriptor: [Intensive Care Units] explode all trees

#15 MeSH descriptor: [Critical Illness] explode all trees

#16 MeSH descriptor: [Respiration, Artificial] explode all trees

#17 MeSH descriptor: [Ventilator Weaning] explode all trees

#18 MeSH descriptor: [Length of Stay] explode all trees

#19 (((mechanical* or artificial) near/2 (ventil* or wean* or respirat*)) or ((crtical* or intens* or emergency) near/2 (care or ill* or patient* or unit* or ward*)) or (length of stay) or ICU):ti,ab

#20 (#13 or #14 or #15 or #16 or #17 or #18 or #19)

#21 (#6 and #12 and #20)

MEDLINE (OvidSP) search strategy

1 protocol* or non?protocol* or directed or guide* or algorithm* or manage* or ((standar* or regular*) adj3 assess*)).mp. or algorithms/ or exp Guideline/ or exp Clinical Protocols/ or exp Medication Therapy Management/

2 exp Conscious Sedation/ or exp Analgesia, Patient-Controlled/ or exp Analgesics/ or exp "Hypnotics and Sedatives"/ or sedat*.af. or analge*.ti,ab.

3 (((mechanical* or artificial) adj4 (ventil* or wean* or respirat*)) or ((crtical* or intens* or emergency) adj5 (care or ill* or patient* or unit* or ward*)) or (length adj3 stay) or ICU).mp. or exp Intensive Care/ or exp Intensive Care Units/ or exp Critical Care/ or exp Critical Illness/ or exp Respiration, Artificial/ or exp Ventilator Weaning/ or "Length of Stay"/

4 ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.

5 1 and 2 and 3 and 4

Embase (OvidSP) search strategy

1 (protocol* or non?protocol* or directed or guide* or algorithm* or manage* or ((standar* or regular*) adj3 assess*)).ti,ab. or algorithm/ or exp practice guideline/ or clinical protocol/ or medication therapy management/

2 conscious sedation/ or exp patient controlled analgesia/ or analgesic agent/ or hypnotic sedative agent/ or sedat*.af. or analge*.ti,ab.

3 (((mechanical* or artificial) adj4 (ventil* or wean* or respirat*)) or ((crtical* or intens* or emergency) adj5 (care or ill* or patient* or unit* or ward*)) or (length adj3 stay) or ICU).ti,ab. or intensive care/ or intensive care unit/ or critical illness/ or artificial ventilation/ or artificial ventilation/ or "length of stay"/

4 (placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab.) not (animals not (humans and animals)).sh.

5 1 and 2 and 3 and 4

CINAHL (EBSCOhost) search strategy

S1. ((MH "Algorithms") OR (MH "Practice Guidelines") OR (MH "Practice Patterns")) OR AB ((protocol* or non?protocol* or directed or guide* or algorithm* or manage* or ((standar* or regular*) and assess*))) OR TI ((protocol* or non?protocol* or directed or guide* or algorithm* or manage* or ((standar* or regular*) and assess*)))
S2. ((MH "Conscious Sedation") OR (MH "Patient-Controlled Analgesia") OR (MH "Analgesics") OR (MH "Hypnotics and Sedatives")) OR AB (sedat* or analge*)
S3. ((MH "Critical Care") OR (MH "Intensive Care Units") OR (MH "Critical Illness") OR (MH "Respiration, Artificial") OR (MH "Ventilator Weaning") OR (MH "Length of Stay")) OR AB ((((mechanical* or artificial) and (ventil* or wean* or respirat*)) or ((crtical* or intens* or emergency) and (care or ill* or patient* or unit* or ward*)) or (length and stay) or ICU))
S4. S1 and S2 and S3
S5. (((MM "Randomized Controlled Trials") OR (MM "Random Assignment") OR (MM "Clinical Trials") OR (MM "Multicenter Studies") OR (MM "Placebos") OR (MM "Prospective Studies") OR (MM "Double-Blind Studies") OR (MM "Single-Blind Studies") OR (MM "Triple-Blind Studies"))) OR AB (random* or ((clinical or controlled) and trial*))
S6. S4 and S5

LILACS (BIREME) search strategy

(protocol$ or non-protocol$ or directed or guide$ or algorithm$ or manage$ or ((standar$ or regular$) and assess$)) and ("sedat$" or "analge$") and ((((mechanical$ or artificial) and (ventil$ or wean$ or respirat$)) or ((crtical$ or intens$ or emergency) and (care or ill$ or patient$ or unit$ or ward$)) or (length and stay) or ICU))

Appendix 2. Study selection form

Study Details		**Comments**
First Author		
Journal / Place of publication		
Year		
Study Eligibility		
Randomized Controlled Trial (RCT)	Yes / No / Unclear	
Relevant participants - Mechanically ventilated - Age > = 18 years	Yes / No / Unclear	
Relevant interventions - Protocol-directed sedation management	Yes / No / Unclear	
Relevant outcomes - Length of mechanical ventilation (hours) - Length of ICU stay - Length of hospital stay - Total dose of sedation - Adverse events (unplanned extubation)	Yes / No / Unclear	

Appendix 3. Data extraction form

	Response	**Comments**
Study ID		
Study authors		
Year of study		
Method		

(Continued)

Country of study		
Level of hospital	Tertiary / Metropolitan / Regional / Rural	
Type of hospital	Public / Private	
Number of beds in hospital		
Type of ICU	Open / Closed / Other	
Number of ICU beds	Medical, n = Surgical, n = Cardiothoracic, n = Cardiology, n = Neurological, n = Trauma, n = Mixed med & surg, n = Other, specify_____, n =	
Usual nurse:patient ratio	1:1 / 1:2 / ≥ 1:3 or greater	
Study design	RCT / Pre-post	
Inclusion criteria applied		
Exclusion criteria applied		
Description of sedation protocol		
Description of 'usual care'		
Usual nurse:patient ratio		
Sedatives used in protocol		
Analgesics used in protocol		
Description of comparator		
Sedatives used in control group		
Analgesics used in control group		
Sedation scale used		
Results	**Intervention Group**	**Control Group**
Numbers of participants enrolled		
Duration of MV	N =	N =

(Continued)

	Duration: mean/median = SD/IQR =	Duration: mean/median = SD/IQR =
Length of ICU stay	N = Length: mean/median = SD/IQR =	N = Length: mean/median = SD/IQR =
Length of hospital stay	N = Length: mean/median = SD/IQR =	N = Length: mean/median = SD/IQR =
Adverse Events	Specify event: _____ n = Specify event: _____ n = Specify event: _____ n = Specify event: _____ n =	Specify event: _____ n = Specify event: _____ n = Specify event: _____ n = Specify event: _____ n =
Incidence of delirium	N =	N =
Memory function – how measured & results?* _____		
Psychological status – how measured & results?* _____		
Cognitive status – how measured & results?* _____		
Quality of life – how measured & results?* _____		
ICU mortality	N =	N =
Hospital mortality	N =	N =
Incidence of tracheostomy	N =	N =

*frequency or mean/median score based on measurement type

Appendix 4. Quality assessment form

Sequence generation		Comments
Method used to generate sequence/group allocation		
Quality of sequence/group allocation	Low risk / High risk / Unclear	
Allocation concealment		
Method used to conceal allocation		
Quality of allocation concealment	Low risk / High risk / Unclear	
Blinding		
Participant	Yes / No / Unsure	
Outcome assessor	Yes / No / Unsure	
Other Specify:	Yes / No / Unsure	
Intention-to-treat		
	Intention-to-treat analysis was applied to all participants entering study	
	15% or fewer excluded	
	More than 15% excluded	
	Not analysed as intention-to-treat	
	Unclear	
Outcome Data		
Was outcome data complete?		
Primary outcome	Yes / No / Unsure	
Secondary outcome 1	Yes / No / Unsure	
Secondary outcome 2 (add more rows if necessary)	Yes / No / Unsure	

WHAT'S NEW

Date	Event	Description
17 December 2018	Amended	Editorial team changed to Cochrane Emergency and Critical Care

HISTORY

Protocol first published: Issue 4, 2012
Review first published: Issue 1, 2015

Date	Event	Description
18 December 2017	New search has been performed	We updated the search and review. The search was run to 18 December 2017.
18 December 2017	New citation required but conclusions have not changed	We included two new studies (Curley 2015; Mansouri 2013). Mansouri 2013 was previously awaiting classification (Aitken 2015).
25 June 2015	Amended	Selective reporting (reporting bias) amended. Previously this section stated that Bucknall 2008 was not registered in a trial register. This has now been corrected (see relevant section).

CONTRIBUTIONS OF AUTHORS

Leanne M Aitken (LA), Tracey Bucknall (TB), Bridie Kent (BK), Marion Mitchell (MM), Elizabeth Burmeister (EB), Samantha J Keogh (SK).

Conceived the review: LA, TB

Designed the review: LA, TB, EB

Co-ordinated the review: LA

Undertook manual searches: LA, TB, EB, SK, BK

Screened search results: LA, TB, BK

Organized retrieval of papers: LA

Screened retrieved papers against inclusion criteria: LA, TB, MM, BK

Appraised quality of papers: LA, TB, MM, EB

Abstracted data from papers: LA, MM, TB, EB, SK

Wrote to authors of papers for additional information: LA

Provided additional data about papers: LA, MM, EB, SK

Obtained and screened data on unpublished studies: LA, MM, EB

Data management for the review: EB, SK

Entered data into Review Manager 5 (Review Manager 2014): EB, LA, SK

Review Manager 5 statistical data (Review Manager 2014): EB, LA, SK

Other statistical analysis not using Review Manager 5 (Review Manager 2014): EB, SK

Double entry of data: data entered by person one: EB; data entered by person two: LA

Interpretation of data: LA, MM TB, EB, BK, SK

Statistical inferences: LA, MM, TB, EB, BK, SK

Wrote the review: LA

Provided guidance on the review: BK

Secured funding for the review: LA

Performed previous work that was the foundation of the present study: LA, TB, MM

Guarantor for the review (one author): LA

People responsible for reading and checking review before submission: TB, BK

DECLARATIONS OF INTEREST

Leanne Aitken (LA) is an author on one of the studies that was excluded from this review (Elliott 2006).

Tracey Bucknall is an author on one of the studies that was included in this review (Bucknall 2008); LA and MM extracted the data from this study.

Bridie Kent: none known

Marion Mitchell: none known

Elizabeth Burmeister: none known

Samantha Keogh is a researcher with the independent research group Alliance for Vascular Access Teaching and Research group (AVATAR) which is supported by competitive government, university, hospital and professional organization research grants as well as industry unrestricted donations, investigator initiated research/educational grants and occasional consultancy payments from the following companies: 3M, Angiodynamics, Baxter, BBraun, BD, Carefusion, Centurion, Cook, Entrotech, Hospira, ResQDevices, Smiths, Teleflex, Vygon. Conducting trial research and systematic reviews is considered part of my role as a senior research fellow.

SOURCES OF SUPPORT

Internal sources

- School of Nursing and Midwifery, Griffith University, Australia.

  Salary of Leanne Aitken, Marion Mitchell and Elizabeth Burmeister
- Princess Alexandra Hospital, Australia.

  Salary of Leanne Aitken, Marion Mitchell and Elizabeth Burmeister
- School of Nursing, Deakin University, Australia.

  Salary of Tracey Bucknall and Bridie Kent
- Alfred Health, Australia.

  Salary of Tracey Bucknall
- NHMRC Centre of Research Excellence in Nursing, Australia.

  Salary of Samantha Keogh
- School of Health Sciences, City University London, UK.

  Salary of Leanne Aitken

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There were only four studies able to be included in this review, and we were unable to pool data for meta-analysis for some outcomes. As a result, there were several differences between the methods that were described in the protocol (Aitken 2012), and the methods used to conduct the review (Aitken 2015). These are listed below.

Objectives

In the protocol, we wrote, "We will look at various outcomes, conduct subgroup and sensitivity analyses and examine the role of bias in order to examine the level of evidence for this intervention". We were limited in the subgroup and sensitivity analyses that could be conducted due to the small number of studies that addressed outcomes of interest.

Types of outcome measures

In the protocol, we identified the following secondary outcomes that were unable to be addressed as no included studies examined them.

1. Total dose of sedation.
2. Incidence of delirium.
3. Memory function.
4. Psychological recovery.
5. Cognitive recovery.
6. Quality of life.

'Summary of findings' table

In the protocol, we stated that we would include duration of mechanical ventilation, length of ICU stay and adverse events in the 'Summary of findings' table. Due to availability of outcome data, we have included duration of mechanical ventilation, ICU mortality, hospital mortality, ICU length of stay, hospital length of stay, incidence of tracheostomy and adverse events (reintubation and self-extubation) in the 'Summary of findings' table.

Assessment of heterogeneity

In the protocol, we said, "We will assess statistical heterogeneity using the I^2 statistic. We will only complete a meta-analysis if the studies are sufficiently homogenous in terms of participants, interventions and outcomes. In the absence of sufficient homogeneity between the studies a descriptive presentation of the results will be provided. Subject to identification of sufficient numbers of studies and appropriate homogeneity, meta-regression may be undertaken." As outlined, we identified statistical heterogeneity for many of the outcomes, therefore, we caution the reader when interpreting these results.

Assessment of reporting biases

In the protocol, we indicated that "If sufficient studies (that is at least 10) meet the criteria to be included in the analysis, we will construct a funnel plot to explore the symmetry of the intervention effects reported by the studies to assess for publication bias". Given that we included only four studies, we were unable to assess for publication bias.

Data synthesis

In the protocol, we stated, "If the studies are sufficiently homogenous a meta-analyses will be conducted using a fixed-effect model. Where there is a significant level of heterogeneity we will use a random-effects model. We will conduct both fixed-effect and random-effects model analyses to check the results before a decision is made as to the most suitable. Analyses will be considered significant at the alpha = 0.05 level. Estimates of precision will be assessed by interpretation of confidence intervals, such as widths, overlapping and inclusion of the null hypothesis." Given the substantial level of statistical heterogeneity, we were unable to conduct meta-analyses for some of the outcomes, or have conducted them but advised care in interpretation, specifically duration of mechanical ventilation, ICU length of stay and incidence of tracheostomy.

Subgroup analysis

In the protocol, we stated, "If we are able to determine details from the studies then subgroup analyses will include the following. Medical, surgical and trauma intensive care patients, as medical patients often have more comorbidities than surgical and trauma patients while trauma patients might have greater need for analgesia, therefore altering the combined sedative effect of the analgesic and sedative agents they are receiving. Nurse-led protocols versus protocols led by other members of the healthcare team (e.g. respiratory therapists) as nurses tend to spend a greater period of time at the bedside and therefore might manage sedation needs differently. Units with 1:1 nurse:patient ratio during usual care versus units with ≥ 1:2 nurse:patient ratio during usual care, as the level of nursing assessment and intervention that is routinely available may influence effect. Patients ventilated via an endotracheal tube versus a tracheostomy tube, as insertion of a tracheostomy tube usually indicates longer-term ventilation plans than management with an endotracheal tube. Age group, as the impact of protocol-directed sedation may vary between different age groups of patients, particularly children compared to adults." Given the

limited number of studies, we were unable to undertake most of these subgroup analyses, but were able to analyse differences in results based on the age group of participants in relation to some outcomes.

Sensitivity analysis

In the protocol, we stated, "We will perform sensitivity analyses to test how sensitive the data are to reasonable changes in the assumptions that are made and in the methods for combining the data. We will test the robustness of the evidence by sensitivity analysis according to randomization (randomized or quasi-randomized) and risk of bias (high, low or unclear). If necessary, we will undertake sensitivity analysis to examine the robustness of effects by excluding specific studies." Given the limited number and methodological variation in the studies, we were unable to undertake these subgroup analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

*Algorithms; *Clinical Protocols; *Conscious Sedation; *Critical Care; *Critical Illness; *Respiration, Artificial; Analgesics [*administration & dosage]; Hospital Mortality; Hypnotics and Sedatives [*administration & dosage]; Length of Stay; Practice Patterns, Nurses'; Publication Bias; Randomized Controlled Trials as Topic; Selection Bias; Time Factors

MeSH check words

Adult; Child; Humans