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Protocol-directed sedation versus non-protocol-directed sedation to reduce duration of mechanical ventilation in mechanically ventilated intensive care patients (Review)

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[Intervention Review]

Protocol-directed sedation versus non-protocol-directed sedation to reduce duration of mechanical ventilation in mechanically ventilated intensive care patients

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ABSTRACT

Background

The sedation needs of critically ill patients have been recognized as a core component of critical care and meeting these is vital to assist recovery and ensure humane treatment. There is growing evidence to suggest that sedation requirements are not always optimally managed. Sub-optimal sedation incorporates both under- and over-sedation and has been linked to both short-term (e.g. length of stay) and long-term (e.g. psychological recovery) outcomes. Various strategies have been proposed to improve sedation management and address aspects of assessment as well as delivery of sedation.

Objectives

To assess the effects of protocol-directed sedation management on the duration of mechanical ventilation and other relevant patient outcomes in mechanically ventilated intensive care unit (ICU) patients. We looked at various outcomes and examined the role of bias in order to examine the level of evidence for this intervention.

Search methods

We searched the Cochrane Central Register of Controlled trials (CENTRAL) (2013; Issue 11), MEDLINE (OvidSP) (1990 to November 2013), EMBASE (OvidSP) (1990 to November 2013), CINAHL (BIREME host) (1990 to November 2013), Database of Abstracts of Reviews of Effects (DARE) (1990 to November 2013), LILACS (1990 to November 2013), Current Controlled Trials and US National Institutes of Health Clinical Research Studies (1990 to November 2013), and reference lists of articles. We re-ran the search in October 2014. We will deal with any studies of interest when we update the review.

Selection criteria

We included randomized controlled trials (RCTs) conducted in adult ICUs comparing management with and without protocol-directed sedation.

Data collection and analysis

Two authors screened the titles and abstracts and then the full-text reports identified from our electronic search. We assessed seven domains of potential risk of bias for the included studies. We examined the 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 (CI).

Main results

We identified two eligible studies with 633 participants. Both 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 one study and unclear for one study. The risk of selection bias related to allocation concealment was low for both studies. We also assessed detection and attrition bias as low for both studies while we considered performance bias high due to the inability to blind participants and clinicians in both studies. Risk due to other sources of bias, such as potential for contamination between groups and reporting bias, was considered unclear. There was no clear evidence of differences in duration of mechanical ventilation (MD -5.74 hours, 95% CI -62.01 to 50.53, low quality evidence), ICU length of stay (MD -0.62 days, 95% CI -2.97 to 1.73) and hospital length of stay (MD -3.78 days, 95% CI -8.54 to 0.97) between people being managed with protocol-directed sedation versus usual care. Similarly, there was no clear evidence of difference in hospital mortality between the two groups (RR 0.96, 95% CI 0.71 to 1.31, low quality evidence). ICU mortality was only reported in one study preventing pooling of data. There was no clear evidence of difference in the incidence of tracheostomy (RR 0.77, 95% CI 0.31 to 1.89). The studies reported few adverse event outcomes; one study reported self extubation while the other study reported re-intubation; given this difference in outcomes, pooling of data was not possible. There was significant heterogeneity between studies for duration of mechanical ventilation (I^2 = 86%, P value = 0.008), ICU length of stay (I^2 = 82%, P value = 0.02) and incidence of tracheostomy (I^2 = 76%, P value = 0.04), with one study finding a reduction in duration of mechanical ventilation and incidence of tracheostomy and the other study finding no difference.

Authors' conclusions

There is currently insufficient evidence to evaluate the effectiveness of protocol-directed sedation. Results from the two RCTs were conflicting, resulting in the quality of the body of evidence as a whole being assessed as low. Further studies, taking into account contextual and clinician characteristics in different ICU environments, 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 duration of mechanical ventilation (method to mechanically assist breathing) in critically ill people.

Background

Determining the sedation needs of critically ill people is an important part of critical care to assist recovery and ensure humane treatment. Protocol-directed sedation is one management strategy that has been proposed as a method of reducing sub-optimal sedation (both under- and over-sedation). Protocol-directed sedation is sedation that is administered by a nurse, pharmacist or other member of the healthcare team according to general principles outlined in a protocol (document). The initial order for protocol-directed sedation is provided by a medical officer or physician. The aim of protocol-directed sedation is to improve patient outcomes, for example reduce the length of time a person requires mechanical ventilation or remains in the intensive care unit.

Search date

The evidence is current to November 2013. We re-ran the search in October 2014. We will deal with any studies of interest when we update the review.

Study characteristics

We searched scientific databases for studies that examined protocol-directed sedation in adult intensive care patients. We identified two studies with 633 participants for inclusion in this review.

Key results

Both included studies compared the use of protocol-directed sedation, specifically protocols delivered by nurses, with usual care (non-protocol-directed sedation). There was no difference in duration of mechanical ventilation, ICU length of stay and hospital length of stay between people managed with protocol-directed sedation and people managed with usual care. Similarly, there was no difference in ICU or hospital deaths between the two groups.

Quality of the evidence

The evidence available to answer our review question is low level, primarily due to the conflicting results that have been reported from the two eligible studies. Further studies need to be conducted to determine the effectiveness of this intervention.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

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

Patient or population: mechanically ventilated ICU patients requiring sedation management
Settings: intensive care unit
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 (hours)	The mean duration of mechanical ventilation across control groups ranged from 93 to 124 hours	The mean duration of mechanical ventilation in the intervention groups was 5.7 hours shorter (62.0 hours shorter to 50.5 hours longer)	-	633 (2 studies)	⊕⊕◯◯ **low** [1,2]	-
ICU mortality	**Medium-risk population**		**RR 1.04** (0.67 to 1.61)	312 (1 study)	⊕⊕◯◯ **low** [3]	-
	201 per 1000	**209 per 1000**				
Hospital mortality	**Medium-risk population**		**RR 0.96** (0.71 to 1.31)	633 (2 studies)	⊕⊕◯◯ **low** [1,4]	-
	289 per 1000	**279 per 1000**				
Adverse event - incidence of re-intubation	**Medium-risk population**		**RR 0.65** (0.35 to 1.24)	321 (1 study)	⊕⊕◯◯ **low** [5]	-
	132 per 1000	**86 per 1000**				

Adverse event - incidence of self extubation	**Medium-risk population**		**RR 2.08** (0.19 to 22.69)	312 (1 study)	⊕⊕◯◯ **low** [6]	-
	6 per 1000	**13 per 1000**				
Incidence of tracheostomy	**Medium-risk population**		**RR 0.77** (0.31 to 1.89)	633 (2 studies)	⊕⊕◯◯ **low** [1,7]	-
	138 per 1000	**114 per 1000**				

*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.

1. Both studies had a high risk of bias in relation to performance bias as neither participants nor personnel were blinded (Brook 1999; Bucknall 2008). There was an unclear risk of bias in relation to selection bias in Brook 1999, as the method of random sequence generation was not clear. Both studies had unclear risk of bias in relation to selective reporting (Brook 1999; Bucknall 2008). Both studies had an unclear risk of other biases, particularly related to whether contamination between the intervention and control groups existed (Brook 1999; Bucknall 2008).
2. There was inconsistency between the results of the two included studies with Brook 1999 finding a significantly shorter length of hospital stay in the experimental group and Bucknall 2008 finding no difference.
3. Only one study reported ICU mortality (Bucknall 2008).
4. Both studies found no difference in mortality, although Brook 1999 had a trend towards favouring the experimental group and Bucknall 2008 had a trend towards the control group suggesting inconsistency in results.
5. Only one study reported incidence of re-intubation (Brook 1999).
6. Only one study reported incidence of self extubation (Bucknall 2008).
7. There is inconsistency between the results of the two included studies with Brook 1999 finding a significantly lower rate of tracheostomy in the experimental group and Bucknall 2008 finding no difference.

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 sub-optimal sedation, ranging from 1% to more than 50% of either sedation time or number of patients (Jackson 2009).

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 compromised long-term psychological recovery, while over-sedation may lead to increased intensive care and hospital lengths of stay and poor long-term recovery (Mehta 2009). 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. 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 2010).

How the intervention might work

Use of a protocol to guide sedation 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). 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. Despite widespread use there is mixed evidence as to their effectiveness.

OBJECTIVES

To assess the effects of protocol-directed sedation management on the duration of mechanical ventilation and other relevant patient outcomes in mechanically ventilated ICU patients. We looked at various outcomes and examined the role of bias in order to examine the level of evidence for this intervention.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) and quasi-randomized controlled trials 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 ICU 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 any protocol that required physician approval for changes in amounts of sedation was excluded. 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. Length of ICU stay.
2. Hospital length of stay.
3. Total dose of sedation.
4. Adverse events (e.g. non-planned extubation).
5. Incidence of delirium.
6. Memory function.
7. Psychological recovery.
8. Cognitive recovery.
9. Quality of life.
10. Incidence of tracheostomy.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled trials (CENTRAL) (2013, Issue 11; see Appendix 1 for search strategy), MEDLINE (OvidSP; from 1990 to November 2013; see Appendix 2 for search strategy), EMBASE (OvidSP; from 1990 to November 2013; see Appendix 3 for search strategy), CINAHL (BIREME host; from 1990 to November 2013; see Appendix 4 for search strategy), Database of Abstracts of Reviews of Effects (DARE) (from 1990 to November 2013), LILACS (1990 to November 2013; see Appendix 5 for search strategy), Current Controlled Trials and US National Institutes of Health Research Studies (from 1990 to November 2013). We re-ran the search in October 2014. We will deal with any studies of interest when we update the review. We used free text and associated exploded subject heading terms for designing our search strategy (see Appendix 2). We chose the inception date of 1990 because no sedation protocols existed before this time.

We combined the MEDLINE search strategy with the Cochrane highly sensitive search strategy, as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We

adapted our MEDLINE search strategy for searching all other databases (see Appendix 2).

We handsearched relevant journals (including online journals) including *American Journal of Respiratory Critical Care*, *Critical Care Medicine*, *Intensive Care Medicine*, *Critical Care* and *American Journal of Critical Care* (1990 to October 2014).

We handsearched reference lists of identified published trials, abstracts of relevant conference proceedings and the reference lists of relevant articles to identify any further clinical trials. We also searched Conference Proceedings Citation Index - Science (CPCI-S), Science Direct (including articles in press), Scopus and Google/Google Scholar. We undertook citation searches of relevant articles through Web of Science and Scopus. We contacted relevant trial authors to identify any additional studies. We did not impose a language restriction.

Searching other resources

We searched specific websites 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.

Data collection and analysis

Selection of studies

Two authors (LA and TB) independently reviewed all titles and decided on the inclusion of studies based on selection criteria (see Appendix 6). We resolved differences and avoided conflicts by consulting a third author (MM).

Data extraction and management

We extracted standardized data from each study using a data extraction form (see Appendix 7). Two authors (LA and TB) independently extracted data for the Brook 1999 study, while two alternate authors (LA and MM) independently extracted data for the Bucknall 2008 study. We designed these differences in extraction processes to avoid conflict of interest due to authorship of an included study (Bucknall 2008). We resolved any disagreements by discussion; if required, we could have consulted with an alternative author (SK), 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 authors (LA and TB or MM) 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 8).

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 (RevMan 2013). 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 source data related to one study, 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

We used the results of intention-to-treat (ITT) analyses for all analyses so all data extracted reflected the original allocation group. There was no evidence of multiple observations or outcome measurements in either 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.

Both included studies had a small number (less than 4%) of participants who were recruited into the studies despite not meeting inclusion criteria (re-admission to ICU, patient awaiting rapid transfer to another ICU) and we excluded these patients from all analyses.

Dealing with missing data

Published study reports identified complete data for all included participants, indicating there were no drop-outs in either study.

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 did not undertake a meta-analysis for that outcome. In the absence of sufficient homogeneity between the studies, we provided a descriptive presentation of the results. We did not undertake meta-regression due to the lack of sufficient numbers of studies and appropriate homogeneity.

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 two 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 planned to use a random-effects model. We did not conduct meta-analyses for many of the outcomes due to the presence of substantial heterogeneity (duration of mechanical ventilation, length of ICU stay and incidence of tracheostomy). We conducted meta-analyses using a random-effects model for the remaining two outcomes of length of hospital stay and hospital mortality. 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). Patients in the study by Brook 1999 were admitted to a medical ICU while patients in the study by Bucknall 2008 were admitted to a general ICU incorporating medical as well as surgical and trauma patients. Given the small number of studies and limited variation in the included participants, we could not undertake sub-group analysis.

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.

'Summary of findings' tables

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. Incidence of tracheostomy.
5. Adverse events (incidence of re-intubation, incidence of self extubation).

We constructed a 'Summary of findings' table using the GRADE software. 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.

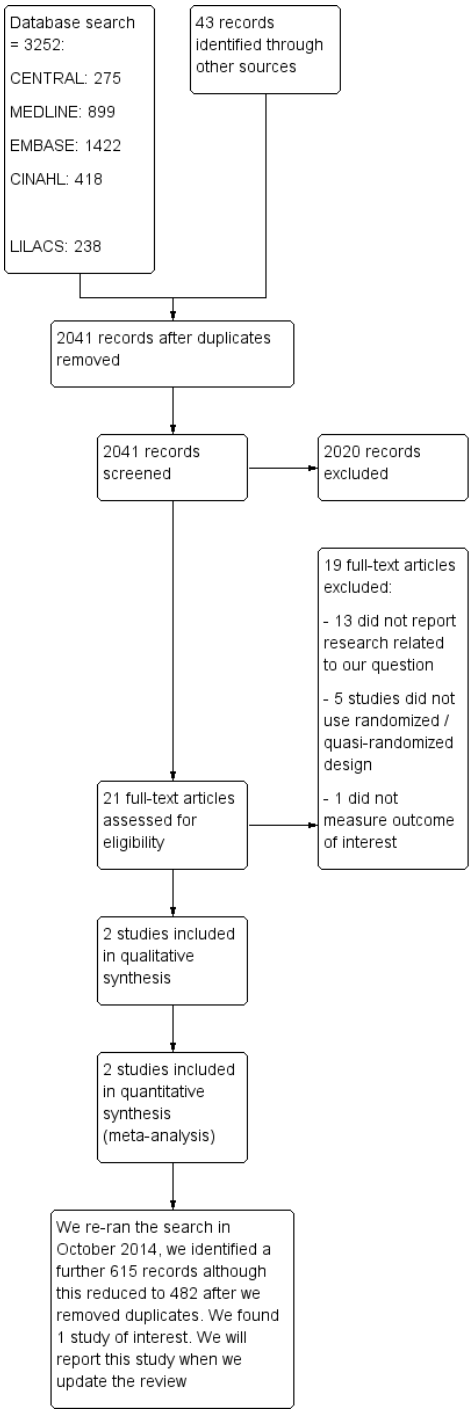
RESULTS

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). We identified 3252 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 2041 records after we removed duplicates. We identified two studies of interest (Brook 1999; Bucknall 2008). We re-ran the search in October 2014. We identified a further 615 records, although this was reduced to 482 when we removed duplicates; we identified one study of interest and we will report this study when we update the review.

Figure 1. Study flow diagram.



Included studies

We included two studies (see Characteristics of included studies table; Brook 1999; Bucknall 2008). The 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.

Population and setting

Brook 1999 enrolled 332 participants 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 re-admitted to the ICU after being in the study previously. Both studies were in closed ICUs with medical care provided by critical care specialists.

Interventions and comparisons

Both studies were single-centre RCTs. The interventions were similar, with Bucknall 2008 indicating they modelled their intervention on that reported by Brook 1999. In both studies, nurses used a structured approach for assessment to determine whether analgesics or sedatives (or both) were required by the patient, then administered pre-specified medications according to their ongoing assessment. Differences in the medications used existed, with Brook 1999 using diazepam, midazolam, fentanyl and morphine, while Bucknall 2008 used midazolam, propofol and morphine.

The most significant difference between the two studies was the usual method of providing sedation-related aspects of care to patients in each of the two study sites. In the 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 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).

Excluded studies

We excluded non-RCTs and studies that did not examine outcomes of interest (see Excluded studies). We identified 2041 records after we had removed duplicates. We retrieved 21 full-text articles. We excluded 13 of these as they did not address our research question, for example they answered different questions or provided a review of the topic, and we excluded six studies as, although they addressed the question of our review, they did not use a randomized or quasi-randomized design. The Characteristics of excluded studies table gives details of studies that did address the question of our review but did not use a randomized or quasi-randomized design.

Risk of bias in included studies

We analysed seven domains of potential risk of bias for the included studies (Figure 2). We rated both studies the same for risk of bias for six of the seven domains. We rated performance bias at high risk, while selection bias was unclear for one study (Brook 1999), and low for the other study (Bucknall 2008). We rated other pre-specified risks at low risk of bias (Figure 3). We judged both studies as having an unclear risk of other bias. There was a lack of description of usual care and nurse : patient ratios in one study (Brook 1999), while both studies had potential for contamination between the two groups (Brook 1999; Bucknall 2008).

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

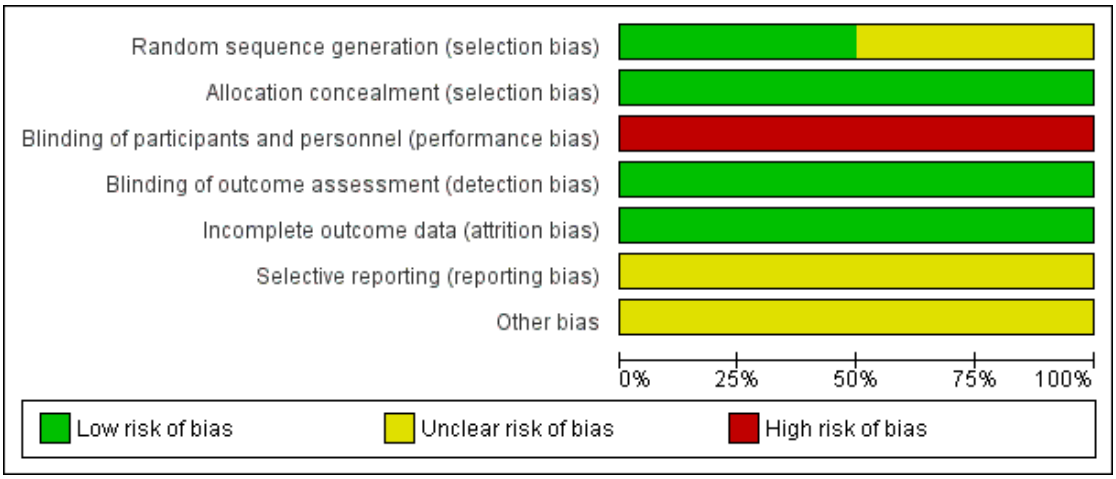
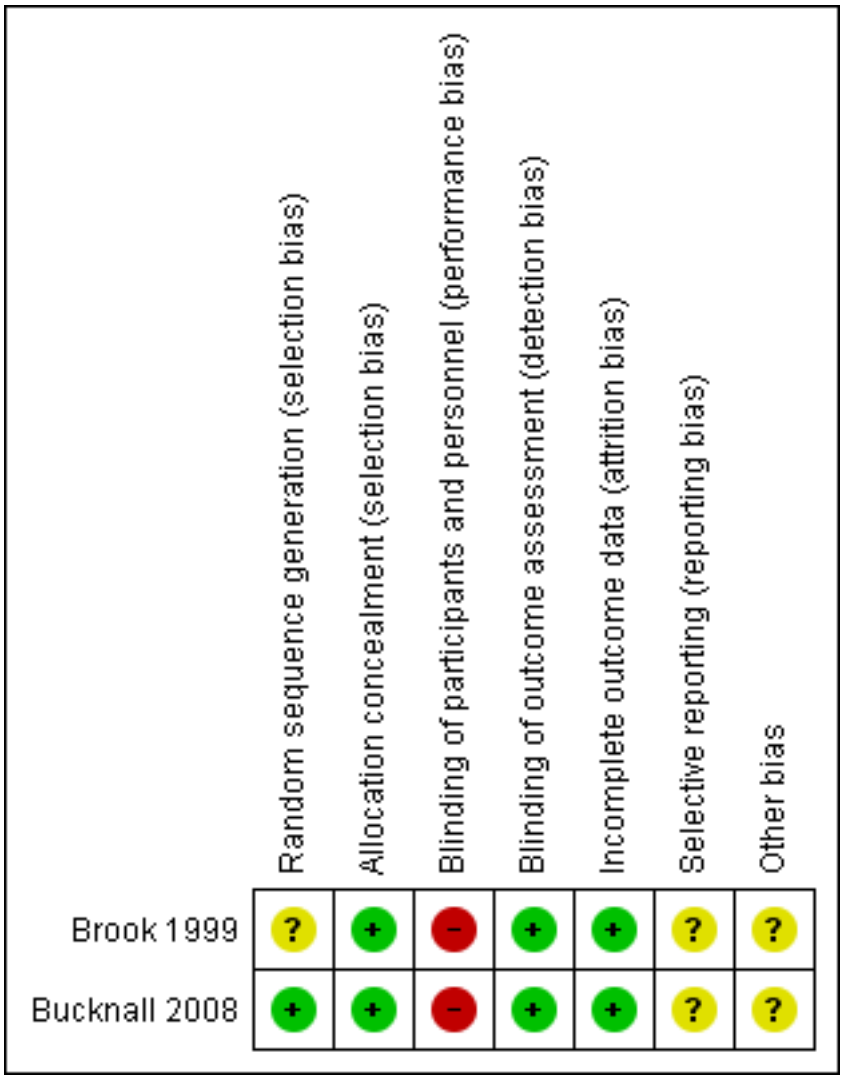


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Both studies used randomization and effective allocation concealment (Brook 1999; Bucknall 2008). One study used computer-generated random sequence (Bucknall 2008); however, the method of random sequence generation in the other study was not described (Brook 1999).

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 both 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).

Incomplete outcome data

Complete outcome data were available for all participants in both studies, resulting in a rating of low risk of attrition bias (Brook 1999; Bucknall 2008).

Selective reporting

Both studies were rated as having an unclear risk of selective reporting bias, with results relating to all specified outcomes being reported (Brook 1999; Bucknall 2008). One study was registered on a relevant trial website (www.ClinicalTrials.gov; NCT00202319) (Bucknall 2008). The other 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

Both studies had an unclear risk of bias due to other potential sources. Of note, usual care was not described well by Brook 1999, except for the number of participants and duration of chemical paralysis. It was unclear if standard management practices (mode of mechanical ventilation, physiotherapy, suctioning, re-positioning, investigations outside 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, re-positioning, investigations outside ICU and need for physical restraints, were not provided. If standard management practices differed between groups, there was a risk of bias.

In addition, a potential for contamination between the two groups existed as participants in both studies 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). 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

Duration of mechanical ventilation

Both included studies reported duration of mechanical ventilation. When we pooled data to analyse the MD receiving mechanical ventilation (MD -5.74 hours, 95% CI -62.01 to 50.53) comparing management with protocol-directed sedation with usual care, the test of heterogeneity was substantial (Tau^2 = 1416.10; Chi^2 = 7.08, degrees of freedom (df) = 1; P value = 0.008; I^2 = 86%) (Analysis 1.1). Such high heterogeneity suggested that the two 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). Interpretation of these results should proceed with caution given this high level of statistical heterogeneity.

Intensive care unit and hospital mortality

Only one study reported ICU mortality data (RR 1.04, 95% CI 0.67 to 1.61) (Bucknall 2008). Both studies reported hospital mortality data. The combined hospital mortality outcome for both studies, with 633 patients, was not significantly different between the protocol-directed sedation and usual care groups (RR 0.96, 95% CI 0.71 to 1.31; heterogeneity Tau^2 = 0.02; Chi^2 = 1.50, df = 1; P value = 0.22; I^2 = 33%) (Analysis 1.2). This level of heterogeneity again suggests the two cohorts may have important differences as outlined above that influence this result.

Length of intensive care unit stay

Both included studies reported length of ICU stay. When we pooled data to analyse the MD in length of ICU stay (MD -0.62 days, 95% CI -2.97 to 1.73) comparing management with protocol-directed sedation with usual care, the test of heterogeneity was substantial (Tau^2 = 2.35; Chi^2 = 5.43, df = 1; P value = 0.02; I^2 = 82%) (Analysis 1.3). Such high heterogeneity suggested that the two studies were very dissimilar, and may reflect the differing nurse : patient ratios present in usual care within the study environments. Interpretation of these results should proceed with caution given this high level of statistical heterogeneity.

Hospital length of stay

Both included studies reported hospital length of stay. The combined MD in hospital length of stay, with 633 patients, was not significantly different between the protocol-directed sedation and usual care groups (MD -3.78 days, 95% CI -8.54 to 0.97) (heterogeneity Tau^2 = 4.83; Chi^2 = 1.67, df = 1; P value = 0.20; I^2 = 40%) (Analysis 1.4). This level of heterogeneity suggests the two cohorts may have important differences as outlined above that influence this result.

Total dose of sedation

We found no studies reporting total dose of sedation.

Adverse events

The studies reported few adverse event data. One study reported re-intubation rates (RR 0.65, 95% CI 0.35 to 1.24) (Brook 1999), while the other study reported self extubation data (RR 2.08, 95% CI 0.19 to 22.69) (Bucknall 2008). In clinical practice, some patients who self extubate will not require re-intubation, therefore self extubation rates would normally be higher than re-intubation rates. In these two studies, Bucknall 2008 reported self extubation rates of only 1% in each group, while Brook 1999 reported re-intubation rates of 6% to 13% in their two groups; this suggests there was substantial heterogeneity between the two cohorts for these adverse events, possibly related to the differing nurse : patient ratios previously described.

Incidence of delirium

We found no studies reporting incidence of delirium.

Memory function

We found no studies reporting memory function.

Psychological recovery

We found no studies reporting psychological recovery.

Cognitive recovery

We found no studies reporting cognitive recovery.

Quality of life

We found no studies reporting quality of life.

Incidence of tracheostomy

The incidence of tracheostomy was reported in both included studies. When we pooled data to analyse the frequency of tracheostomy (RR 0.77, 95% CI 0.31 to 1.89) comparing management with protocol-directed sedation with usual care, the test of heterogeneity was substantial (Tau^2 = 0.32; Chi^2 = 4.16, df = 1; P value = 0.04; I^2 = 76%) (Analysis 1.5). Such high heterogeneity suggested that the two studies were very dissimilar, and may reflect the differing nurse : patient ratios present in usual care within the study environments. Interpretation of these results should proceed with caution given this high level of statistical heterogeneity.

Secondary outcomes that were reported in both studies included ICU and hospital length of stay as well as incidence of tracheostomy. There was no difference in duration of hospital length of stay between participants who received protocol-directed sedation and participants 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.

DISCUSSION

Summary of main results

We identified two RCTs with 633 participants 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 mortality with protocol-directed sedation in the USA study, while Bucknall 2008 reported no difference in either outcome in the Australian study. When we pooled data, 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.

Overall completeness and applicability of evidence

The two studies included in this systematic review both reported the data regarding our primary outcomes; however, data relating to only a few of our secondary outcomes were reported. Importantly, neither 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, 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 one study being conducted in the USA in the 1990s (Brook 1999), while the other study was conducted in Australia approximately 10 years later (Bucknall 2008). These differences in geographic location and time 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 two settings was the usual nurse : patient ratio, with each nurse caring for two or three patients in the USA setting, while each nurse cared for one mechanically ventilated patient in the Australian setting; 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.

Quality of the evidence

The methodological quality of the studies included in this review was moderate, but the quality of the overall evidence was low. We only included two studies and they had conflicting results resulting in wide CIs for some outcomes. Furthermore, although we rated studies as having a low risk of detection and attrition bias and some aspects of selection bias, one or both 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.

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 any included study, we removed them from the process of analysing relevant 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 two studies included in this review (Brook 1999; Bucknall 2008), 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 but no difference in length of stay (Brattebo 2002) and two French studies identified a reduction in duration of mechanical ventilation (De Jonghe 2005; Quenot 2007). We found no additional studies conducted in North America. 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, 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. Both included studies measured doses of sedative agents but few differences were noted and no total dose of sedation was available to enable comparisons (Brook 1999, Bucknall 2008). It is unlikely that any meaningful comparison of sedative agents could be made given the effect of factors such as patient weight, and renal and liver function on drug metabolism.

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 two included RCTs reported conflicting results 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. There was no evidence to draw conclusions on the efficacy and safety of protocol-directed sedation, although 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

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. 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 design such as cluster randomization 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).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Brook 1999

Methods	Randomized, controlled clinical trial
Participants	Setting: university-affiliated urban teaching hospital in USA; closed medical ICU (19 beds); nurse : patient ratio - 2 : 1 to 3 : 1 Participants: 332 patients requiring mechanical ventilation were randomized; 4 patients 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 patients 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 vs. 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 vs. 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 sedatives. 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 was duration of mechanical ventilation. Secondary outcomes included ICU and hospital lengths of stay, hospital mortality, rates of development of organ system derangements, re-intubation and 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

Brook 1999 (*Continued*)

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 patients 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 patients. Incomplete data from 106 participants who died and were not successfully waned 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 pre-specified post-hoc analysis
Selective reporting (reporting bias)	Unclear risk	No registration of study or publication of study protocol; however, all primary and secondary outcomes results and pre-specified 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, re-positioning, 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 Baseline participant characteristics were described as similar between groups, with variables

Brook 1999 (*Continued*)

		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, control group had a higher trend for the number of participants with pneumonia (34 participants in protocol group vs. 47 participants in usual care group, P value = 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: metropolitan teaching hospital in Australia; closed general ICU (24 beds); nurse : patient ratio 1 : 1 Participants: 316 mechanically ventilated ICU patients were randomized in the study. 4 patients were excluded from final analysis due to inappropriate re-enrolment into the study following re-admission to ICU. 312 patients 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 vs. 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: time from commencement of mechanical ventilation in the ICU to successful weaning from mechanical ventilation Secondary outcomes: duration of ICU and hospital length of stay, ICU and hospital mortality, rates of self extubation and 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
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 & 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 re-admission to ICU. Outcome data were provided for the remaining 312 participants and included in final analysis
Selective reporting (reporting bias)	Unclear 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, re-positioning, 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

Abbreviations:
APACHE: Acute Physiology and Chronic Health Evaluation; COPD: chronic obstructive pulmonary disease; ICU: intensive care unit; SAPS: Simplified Acute Physiology Score.

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

Study	Reason for exclusion
Arias-Rivera 2008	Not an RCT, was a before-after prospective study of the effect of introducing nurse-directed sedation
Brattebo 2002	Not an RCT, was a pre-intervention, post-intervention observational study of the effect of introducing protocol-directed sedation
De Jonghe 2005	Not an RCT, was a 2-phase prospective controlled study examining the effect of protocol-directed sedation
Elliott 2006	Not an RCT, was a pre-intervention, post-intervention comparative investigation of the effect of protocol-directed sedation
Quenot 2007	Not an RCT, was a 2-phase (before-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.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Mansouri 2013

Methods	Randomized controlled trial
Participants	201 mixed medical-surgical ICU patients
Interventions	Protocol-directed management of pain, agitation and delirium
Outcomes	Duration of mechanical ventilation, length of ICU stay, mortality
Notes	

ICU: intensive care unit.

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	2	633	Mean Difference (IV, Random, 95% CI)	-5.74 [-62.01, 50.53]
2 Hospital mortality	2	633	Risk Ratio (IV, Random, 95% CI)	0.96 [0.71, 1.31]
3 Intensive care unit length of stay	2	633	Mean Difference (IV, Random, 95% CI)	-0.62 [-2.97, 1.73]
4 Hospital length of stay	2	633	Mean Difference (IV, Random, 95% CI)	-3.78 [-8.54, 0.97]
5 Incidence of tracheostomy	2	633	Risk Ratio (IV, Random, 95% CI)	0.77 [0.31, 1.89]

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

Review: Protocol-directed sedation versus non-protocol-directed sedation to reduce duration of mechanical ventilation in mechanically ventilated intensive care patients

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

Outcome: 1 Duration of mechanical ventilation

Study or subgroup	Protocolized sedation		Usual care		Mean Difference	Weight	Mean Difference
	N	Mean(SD)[hours]	N	Mean(SD)[hours]	IV,Random,95% CI		IV,Random,95% CI
Brook 1999	162	89.1 (133.6)	159	124 (153.6)		49.2 %	-34.90 [-66.42, -3.38]
Bucknall 2008	153	115.92 (146.6)	159	93.39 (103.2)		50.8 %	22.53 [-5.70, 50.76]
Total (95% CI)	**315**		**318**			**100.0 %**	**-5.74 [-62.01, 50.53]**

Heterogeneity: Tau^2 = 1416.10; Chi^2 = 7.08, df = 1 (P = 0.01); I^2 =86%

Test for overall effect: Z = 0.20 (P = 0.84)

Test for subgroup differences: Not applicable

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

Review: Protocol-directed sedation versus non-protocol-directed sedation to reduce duration of mechanical ventilation in mechanically ventilated intensive care patients

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

Outcome: 2 Hospital mortality

Study or subgroup	Protocolized sedation n/N	Usual care n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Brook 1999	49/162	57/159		57.9 %	0.84 [0.62, 1.15]
Bucknall 2008	39/153	35/159		42.1 %	1.16 [0.78, 1.73]
Total (95% CI)	**315**	**318**		**100.0 %**	**0.96 [0.71, 1.31]**

Total events: 88 (Protocolized sedation), 92 (Usual care)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 1.50$, df = 1 (P = 0.22); $I^2 = 33\%$

Test for overall effect: Z = 0.23 (P = 0.81)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Protocol-directed sedation management compared with usual care, Outcome 3 Intensive care unit length of stay.

Review: Protocol-directed sedation versus non-protocol-directed sedation to reduce duration of mechanical ventilation in mechanically ventilated intensive care patients

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

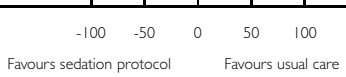
Outcome: 3 Intensive care unit length of stay

Study or subgroup	Protocolized sedation N	Mean(SD)[days]	Usual care N	Mean(SD)[days]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Brook 1999	162	5.7 (5.9)	159	7.5 (6.5)		50.9 %	-1.80 [-3.16, -0.44]
Bucknall 2008	153	6.6 (7.2)	159	6 (6.2)		49.1 %	0.60 [-0.89, 2.09]
Total (95% CI)	**315**		**318**			**100.0 %**	**-0.62 [-2.97, 1.73]**

Heterogeneity: $Tau^2 = 2.35$; $Chi^2 = 5.43$, df = 1 (P = 0.02); $I^2 = 82\%$

Test for overall effect: Z = 0.52 (P = 0.60)

Test for subgroup differences: Not applicable



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

Review: Protocol-directed sedation versus non-protocol-directed sedation to reduce duration of mechanical ventilation in mechanically ventilated intensive care patients

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

Outcome: 4 Hospital length of stay

Study or subgroup	Protocolized sedation		Usual care		Mean Difference	Weight	Mean Difference
	N	Mean(SD)[days]	N	Mean(SD)[days]	IV,Random,95% CI		IV,Random,95% CI
Brook 1999	162	14 (17.3)	159	19.9 (24.2)		56.8 %	-5.90 [-10.51, -1.29]
Bucknall 2008	153	18.2 (19.2)	159	19.2 (31.9)		43.2 %	-1.00 [-6.82, 4.82]
Total (95% CI)	**315**		**318**			**100.0 %**	**-3.78 [-8.54, 0.97]**

Heterogeneity: $Tau^2 = 4.83$; $Chi^2 = 1.67$, df = 1 (P = 0.20); $I^2 = 40\%$

Test for overall effect: Z = 1.56 (P = 0.12)

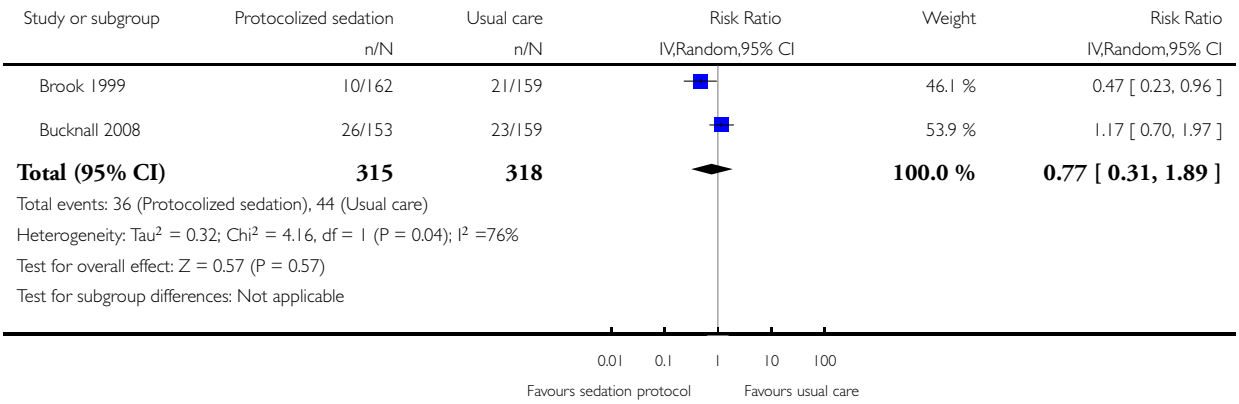
Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Protocol-directed sedation management compared with usual care, Outcome 5 Incidence of tracheostomy.

Review: Protocol-directed sedation versus non-protocol-directed sedation to reduce duration of mechanical ventilation in mechanically ventilated intensive care patients

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

Outcome: 5 Incidence of tracheostomy



APPENDICES

Appendix 1. 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 Intensive Care explode all trees
#14 MeSH descriptor Intensive Care Units explode all trees
#15 MeSH descriptor Critical Care explode all trees
#16 MeSH descriptor Critical Illness explode all trees
#17 MeSH descriptor Respiration, Artificial explode all trees
#18 MeSH descriptor Ventilator Weaning explode all trees
#19 MeSH descriptor Length of Stay explode all trees

#20 (#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)
#21 (#6 AND #12 AND #20)

Appendix 2. 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. 1 and 2
4. (((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"/
5. 3 and 4
6. ((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.
7. 5 and 6

Appendix 3. 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. 1 and 2 and 3
5. (placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab.) not (animals not (humans and animals)).sh.
6. 4 and 5

Appendix 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. S5 and S4

Appendix 5. 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 6. 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 7. Data extraction form

	Response	Comments
Study ID		
Study authors		
Year of study		
Method		
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		

(*Continued*)

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 = Duration: mean/median = SD/IQR =	N = 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?* _____			

(*Continued*)

ICU mortality	N =	N =	
Hospital mortality	N =	N =	
Incidence of tracheostomy	N =	N =	

*frequency or mean/median score based on measurement type

Appendix 8. 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	

(*Continued*)

	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

Last assessed as up-to-date: 18 November 2013.

Date	Event	Description
25 June 2015	Amended	Selective reporting (reporting bias) amended. Previously this section stated stated that Bucknall 2008 was not registered on 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.

Screened search results: LA, TB.

Organized retrieval of papers: LA.

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

Appraised quality of papers: LA, TB, MM.

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

Wrote to authors of papers for additional information: LA.

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

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

Data management for the review: EB.

Entered data into Review Manager 5 (RevMan 2013): EB.

Review Manager 5 statistical data (RevMan 2013): EB.

Other statistical analysis not using Review Manager 5 (RevMan 2013): EB.

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 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).

Bridie Kent: none known.

Marion Mitchell: none known.

Elizabeth Burmeister: none known.

Samantha Keogh: none known.

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 two 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 this review. 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 unable to conduct subgroup and sensitivity analyses due to the limited 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, incidence of tracheostomy and adverse events (re-intubation 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 provided a descriptive presentation of the results. We did not undertake meta-regression.

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 two 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, specifically duration of mechanical ventilation, length of ICU 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 co morbidities 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 health care 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 $\geq$ 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 these subgroup analyses.

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.

NOTES

June 25 2015: Selective reporting (reporting bias) amended. Previously this section stated that Bucknall 2008 was not registered on a trial register. This has now been corrected (see relevant section).