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Practice patterns and outcomes associated with early sedation depth in mechanically ventilated patients: a systematic review protocol

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TITLE: Practice patterns and outcomes associated with early sedation depth in mechanically ventilated patients: a systematic review protocol

REGISTRATION: This systematic review has been registered with the PROSPERO international prospective register of systematic reviews (#57264)

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ABSTRACT

Introduction: Mechanical ventilation is a commonly performed intervention in critically ill patients. Frequently, these patients experience deep sedation early in their clinical course. Emerging data suggest that the practice of early deep sedation may negatively impact patient outcomes. The purpose of this review is to assess the world's literature to describe and determine the impact of early deep sedation on the outcomes of mechanically ventilated patients.

Methods and analysis: Randomized controlled trials and non-randomized studies will be eligible for inclusion in this systematic review. With the assistance of a medical librarian, we will comprehensively search MEDLINE, EMBASE, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews and Effects (DARE), and Cochrane Database of Systematic Reviews for peer reviewed literature. Grey literature from Society of Critical Care Medicine, European Society of Intensive Care Medicine, International Symposium on Intensive Care and Emergency Medicine, American Thoracic Society, Society for Academic Emergency Medicine, and Pharmacotherapy meetings between 2010 to 2017 will be reviewed manually. Two authors will independently review all search results and disagreements will be resolved through arbitration by a third author. If appropriate, meta-analysis will be used for quantitative analysis of the data. Heterogeneity between studies will be assessed using the I^2 statistic.

Ethics and dissemination: The proposed systematic review will not collect data that is associated with individual patients and does not require ethical approval. Results of this study will contribute to the understanding of early sedation, identify future research targets, and guide early care in mechanically ventilated patients.

ARTICLE SUMMARY

Strengths and Limitations

- This is the first systematic review specifically studying the impact of early sedation depth on patient important outcomes
- In preparation of this protocol we followed the PRISMA-P guidelines and our study is registered with the PROSPERO international prospective register of systematic reviews.
- Our robust search strategy will decrease our risk of missing relevant studies.
- Our inclusion of non-randomized trials increases the risk of study bias.

Keywords: Sedation, Mechanical ventilation, Systematic Review, Meta-analysis

TEXT

INTRODUCTION

Mechanically ventilation is a common intervention in critically ill patients[1]. There is increasing recognition that the management of non-ventilator related aspects of care is highly influential on outcome. The management of sedation plays a major role in the care of mechanically ventilated patients[2]. While necessary to relieve pain and anxiety and improve tolerance of mechanical ventilation, sedatives have adverse effects on important patient-centered outcomes, such as lengths of stay, delirium, and mortality[3 4]. Present guidelines recommend that sedatives be titrated to achieve light, as opposed to deep, levels of sedation[2].

Despite these recommendations, deep sedation in the intensive care unit (ICU) is common. Specifically, early deep sedation (i.e. during the first 48 hours following initiation of mechanical ventilation) occurs in up to 76% of patients[5 6]. An emerging body of research suggests that the level of sedation during this early time period is an independent predictor of patient outcomes[7 8]. However, the bulk of prior sedation research has not been devoted to this initial early period, often not enrolling patients until after 48 hours of mechanical ventilation[6].

While the available evidence supports maintenance of early light sedation, the strength of the association remains unclear.

There have been no systematic reviews on the impact of early sedation on clinical outcomes. An important next step for investigating early sedation practices is to analyze the world literature to ascertain the true impact of early sedation. In this systematic review, we seek to 1) describe the state of global literature focusing on early sedation; and 2) quantify the impact of early sedation depth on patient-centered outcomes. We hypothesize that deep sedation in the 48 hour period follow initiation of mechanical ventilation will be associated with increased mortality and longer lengths of stay.

METHODS AND ANALYSIS

Protocol and registration

This systematic review protocol is prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement (online supplementary additional file 1)[9 10]. The final results will be reported according to PRISMA and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines[11 12]. Any deviation from the protocol will be reported with the final results, along with a rationale for protocol deviation. This systematic review has been registered in the PROSPERO international prospective register of systematic reviews (#57264).

Search for and identification of studies

An electronic search will include the following databases: MEDLINE, EMBASE, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews and Effects (DARE), and Cochrane Database of Systematic Reviews. The search terms include the concepts of mechanical ventilation, sedation depth, critical illness, and outcome measures (including delirium, mortality, length of stay, tracheostomy, time to extubation, and time ventilated). These strategies were established using a combination of standardized terms and

key words. The fully reproducible search strategy is provided in the online supplementary additional file 2. The search was designed in cooperation with a medical librarian, who performed the electronic search.

The reference lists of the articles selected for inclusion will be manually screened to identify additional studies. To identify potential unpublished data, abstracts from the following meetings (from 2010 to 2017) will be manually searched: Society of Critical Care Medicine, European Society of Intensive Care Medicine, International Symposium on Intensive Care and Emergency Medicine, American Thoracic Society, Society for Academic Emergency Medicine, and Pharmacotherapy. An online search for details of clinical trials registration (ClinicalTrials.gov) will also be conducted to identify completed, but not yet published, clinical studies. The principal investigators of published and unpublished studies will also be contacted as needed for clarification of potential data for inclusion.

Eligibility criteria

Studies will be eligible regardless of language, and will include adult patients receiving invasive positive pressure ventilation. Randomized controlled trials (RCT), as well as non-randomized studies (prospective and retrospective cohort analyses, cross-sectional studies, before-after trials) will be included. Non-randomized studies will be included for the following reasons: 1) a likelihood that the question of interest may not be investigated strictly with RCTs secondary to a lack of existing randomized trials; 2) to provide an explicit evaluation of strengths and weaknesses of the current literature; 3) to assess evidence of effects (benefit and harm); and 4) to provide evidence for the undertaking of randomized trials. Papers that are reviews, correspondences, editorials, and non-human studies will be excluded. Eligibility criteria are listed in Table 1.

The intervention will be the sedation provided during the first 48 hours of mechanical ventilation. The comparison will be sedation depth (light sedation versus deep sedation). Eligible studies must report some objective measure of sedation depth, such as the Richmond Agitation-

Sedation Scale (RASS) or the Glasgow Coma Scale (GCS). The clinical outcomes will be assessed according to sedation depth. These include: mortality, delirium, ventilator-free days, hospital and ICU lengths of stay, and incidence of tracheostomy. The drugs used for early sedation will also be qualitatively reported, as will the study location (i.e. ICU, emergency department). If there is a relative paucity of data describing early sedation, we will also qualitatively report the sedation provided at trial enrollment for RCTs. Similarly, we will report the depth of sedation at the time of trial enrollment for RCTs.

Study selection and data abstraction

Two independent reviewers will screen titles and abstracts of identified studies for eligibility. After this relevance screen, the two reviewers will compare their included studies to determine if disagreement exists. In cases of disagreement, the opinion of a third reviewer will be sought and a consensus will be reached. Full text articles will then be obtained and these manuscripts will be reviewed for potential inclusion.

The same two reviewers will extract data using standardized forms. The following data on study characteristics will be collected and placed in a table: author, year of publication, study design, number of patients included, characteristics of the patient population, sedation data, study quality, risk of bias, and outcomes. We will include pertinent study-specific comments in the table as needed.

Assessment of study quality

We will assess quality of clinical trials using the Cochrane Collaboration's tool for assessing the risk of bias in clinical trials and report a summary assessment for the risk of bias for each studied outcome[13]. For studies of observational design, quality will be assessed with the Newcastle Ottawa Scale, assigning a maximum of nine points. Five or fewer points will indicate a high risk of bias[14].

Assessment of publication bias

A graphical display (funnel plot) of the size of the treatment effect against the precision of the trial will be used to evaluate for potential publication bias.

Strategy for data synthesis

We will provide a comprehensive narrative synthesis and qualitative analysis of the data, structured around outcomes related to sedation. After conducting the systematic review, if the data can be pooled, we will use a meta-analytic approach to quantitatively analyze the data. A random effects model will be used to calculate pooled effect sizes and corresponding 95% confidence intervals [CI] between deep and light sedation groups. Odds ratios will be calculated for binary data, such as mortality comparisons. Continuous outcomes will be reported as mean difference, and overall effect estimates will be generated using a Z test and presented as mean differences. A p value of < 0.05 will be considered statistically significant.

Heterogeneity between studies will be assessed using the I^2 statistic, with suggested thresholds for low (25-49%), moderate (50-74%), and high (≥75%) values[15].

We will perform sensitivity and subgroup analyses if the systematic review suggests that this is feasible and warranted to explore heterogeneity between studies.

ETHICS AND DISSEMINATION

As this is a systematic review of completed studies, no ethical approval will be required. Results from this systematic review will be submitted for publication in peer-reviewed journals, and will be presented at national meetings.

This study will refine the understanding of the impact of early sedation practices and inform healthcare workers providing care to mechanically ventilated patients. We anticipate that this information will improve the post-intubation care received by mechanically ventilated patients.

DISCUSSION

Over the past decade, there has been an increasing recognition that early advanced care has significant impact on patient outcome during critical illness. This concept has been

shown to be true with regard to antibiotics in sepsis, lung protective ventilation in respiratory failure, and reperfusion therapy in cerebrovascular accident[16-18]. However, there has not been a similar focus on early sedation care for patients treated with mechanical ventilation.

This systematic review will provide a complete synopsis of the world's literature examining the impact of early deep sedation on patient outcomes, including mortality and lengths of stay. We will assess the cohort of studies for study quality, publication bias, heterogeneity, and determine if a meta-analysis is appropriate. We expect to find that early deep sedation is associated with worse mortality, longer lengths of stay, and greater ventilation duration. Furthermore, we will identify knowledge gaps in the literature as future research targets.

In conclusion, this systemic review will aim to characterize and quantify the impact of early sedation on patient important outcomes. We hope this study yields additional evidence to guide clinical practice in mechanically ventilated patients, as well as targets for future investigation.

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AUTHOR CONTRIBUTIONS:
RJS: Study conception and design, drafting the manuscript, critical revision, guarantor of the review
MRD: Drafting the manuscript, critical revision
BWR: Study design, drafting the manuscript, critical revision
SAF: Study design, devising the search strategy
BMF: Study conception and design, drafting the manuscript, critical revision

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COMPETING INTERESTS STATEMENT:

All authors declare that they have no significant competing financial, professional, or personal interests that may influence the performance or presentation of this study.

Table 1. Eligibility criteria for inclusion in systematic review

	Inclusion Criteria	Exclusion Criteria
Population	• Age ≥ 18 years	• Age < 18 years
Intervention	• Invasive positive pressure ventilation	• Chronic ventilation
Reference Standard	• Objective measure of sedation depth	• None
Outcomes	• Mortality • Hospital length of stay • ICU length of stay • Time to extubation • Delirium • Incidence of tracheostomy	• None
Study Design	• Randomized controlled trials • Prospective cohort studies • Retrospective cohort studies • Cross-sectional studies • Before-after trials	• Correspondences • Editorials • Non-human studies

Prepared by:

Susan A. Fowler, MLIS
Bernard Becker Medical Library
Washington University in St. Louis

Methods section text:

The published literature was searched using strategies created by a medical librarian for the concepts of mechanical ventilation, sedation depth, critical illness, and outcome measures including delirium, mortality, length of stay, tracheostomy, time to extubation, and time ventilated. These strategies were established using a combination of standardized terms and key words. To exclude animals, SF used the Human filter for Medline recommended in Cochrane Handbook for Systematic Reviews of Interventions and modified it to create similar filters for the other databases searched. Database platforms searched include Ovid Medline 1946-, Embase.com 1947-, Scopus.com 1823-, Wiley Cochrane Central Register of Controlled Trials (CENTRAL), Wiley Database of Abstracts of Reviews of Effects (DARE), and Wiley Cochrane Database of Systematic Reviews. All searches were completed in October 2016. All results were exported to EndNote. We used the automatic duplicate finder in EndNote and hand searched for duplicates as well to accurately identify and remove duplicates resulting in a total of 946 unique citations. Clinicaltrials.gov was also searched with a total of 8 resulting trials. Full search strategies are provided.

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

Search Strategies

Ovid Medline
Date Searched: 10/11/2016
Applied Database Supplied Limits: 0
Number of Results: 446

Full Search Strategy:

(exp Respiration, Artificial/ OR (Respironics V60 OR Servo-I OR Tangens 2C).mp. OR ((mechanical* OR artificial*) ADJ2 (ventilat* OR respirat*).mp.) OR (ventilat* adj8 patient*).mp.) AND (exp Critical Illness/ OR Critical Care/ OR exp Intensive Care Units/ OR Emergencies/ OR exp Emergency Service, Hospital/ OR Emergency Medicine/ OR (critical* adj3 ill*).mp. OR ((intensive OR subacute OR critical) adj3 (care OR therap*)).mp. OR emergenc*.mp. OR ((accident OR trauma OR urgent) adj2 (service* OR center* OR centre* OR dispensary)).mp.) AND (exp Deep Sedation/ OR exp Conscious Sedation/ OR ((moderate OR conscious OR light* OR deep OR depth* OR level*) ADJ3 sedat*).mp.) AND (exp Delirium/ OR exp Mortality/ OR exp "Length of Stay"/ OR exp Tracheostomy/ OR (delirium* OR delirious OR delire OR delier OR mortal* OR death* OR died OR fatal* OR Tracheostom*).mp. OR ((length OR time OR day* OR hospital OR unit) adj5 (stay* OR discharge* OR duration)).mp. OR ((time* OR delay*) adj2 (extubat*)).mp. OR ((prolong* OR duration OR day*) adj5 (ventilat*)).mp.) not ((exp Animals/) not (exp Animals/ and exp Humans/))

Embase
Date Searched: 10/11/2016
Applied Database Supplied Limits: 0
Number of Results: 608

Full Search Strategy:

('mechanical ventilator'/exp OR 'artificial ventilation'/exp OR 'Respironics V60' OR 'Servo-I' OR 'Tangens 2C' OR 'ventilated patient'/exp OR (mechanical* OR artificial*) NEAR/2 (ventilat* OR respirat*) OR (ventilat* NEAR/8 patient*)) AND ('critically ill patient'/exp OR 'intensive care'/de OR 'emergency health service'/exp OR 'emergency ward'/exp OR 'emergency'/exp OR 'emergency medicine'/exp OR critical* NEAR/3 ill* OR (intensive OR subacute OR critical) NEAR/3 (care OR therap*) OR emergenc* OR (accident OR trauma OR urgent) NEAR/2 (service* OR center* OR centre* OR dispensary)) AND ('conscious sedation'/exp OR 'deep sedation'/exp OR (moderate OR conscious OR light* OR deep OR depth* OR level*) NEAR/3 sedat*) AND ('delirium'/exp OR 'mortality'/exp OR 'length of stay'/exp OR 'hospital discharge'/exp OR 'tracheostomy'/exp OR delirium* OR delirious OR delire OR delier OR mortal* OR death* OR died OR fatal* OR Tracheostom* OR (length OR time OR days OR hospital OR unit) NEAR/5 (stay* OR discharge* OR duration) OR (time* OR delay*) NEAR/2 extubat* OR (prolong* OR duration OR day*) NEAR/5 ventilat*) NOT ([animals]/lim NOT [humans]/lim)

Cochrane
Date Searched: 10/17/2016
Applied Database Supplied Limits: 0
Number of Results from each database in Cochrane
CDSR: 39
CENTRAL: 116
DARE: 6

Full Search Strategy:

([mh "Respiration, Artificial"] OR 'Respironics V60' OR 'Servo-I' OR 'Tangens 2C' OR ((mechanical* OR artificial*) NEAR/2 (ventilat* OR respirat*)) OR (ventilat* NEAR/8 patient*)) AND ([mh "Critical Illness"] OR [mh ^"Critical Care"] OR [mh "Intensive Care Units"] OR [mh ^"Emergencies"] OR [mh "Emergency Service, Hospital"] OR [mh "Emergency Medicine"] OR (critical* NEAR/3 ill*) OR ((intensive OR subacute OR critical) NEAR/3 (care OR therap*)) OR emergenc* OR ((accident OR trauma OR urgent) NEAR/2 (service* OR center* OR centre* OR dispensary))) AND ([mh "Deep Sedation"] OR [mh "Conscious Sedation"] OR ((moderate OR conscious OR light* OR deep OR depth* OR level*) NEAR/3 (sedat*))) AND ([mh "Delirium"] OR [mh "Mortality"] OR [mh "Length of Stay"] OR [mh "Tracheostomy"] OR delirium* OR delirious OR delire OR delier OR mortal* OR death* OR died OR fatal* OR ((length OR time OR days OR hospital OR unit) NEAR/5 (stay* OR discharge* OR duration)) OR Tracheostom* OR

((time* OR delay*) NEAR/2 (extubat*)) OR ((prolong* OR duration OR day*) NEAR/5 (ventilat*))) NOT (([mh “Animals”]) NOT ([mh “Animals”] AND [mh “Humans”]))

Scopus
Date Searched: 10/17/2016
Applied Database Supplied Limits: 0
Number of Results: 591

Full Search Strategy:

(TITLE-ABS-KEY("Respironics V60" OR "Servo-I" OR "Tangens 2C") OR TITLE-ABS-KEY((mechanical* OR artificial*) W/2 (ventilat* OR respirat*)) OR TITLE-ABS-KEY(ventilat* W/8 patient*)) AND (TITLE-ABS-KEY(critical* W/3 ill*) OR TITLE-ABS-KEY((intensive OR subacute OR critical) W/3 (care OR therap*)) OR TITLE-ABS-KEY(emergenc*) OR TITLE-ABS-KEY((accident OR trauma OR urgent) W/2 (service* OR center* OR centre* OR dispensary))) AND (TITLE-ABS-KEY((moderate OR conscious OR light* OR deep OR depth* OR level*) W/3 (sedat*))) AND (TITLE-ABS-KEY(delirium* OR delirious OR delire OR delier OR mortal* OR death* OR died OR fatal*) OR TITLE-ABS-KEY((length OR time OR days OR hospital OR unit) W/5 (stay* OR discharge* OR duration)) OR TITLE-ABS-KEY(Tracheostom*) OR TITLE-ABS-KEY((time* OR delay*) W/2 (extubat*)) OR TITLE-ABS-KEY ((prolong* OR duration OR day*) W/5 (ventilat*))) AND KEY(human OR humans OR woman OR man OR women OR men OR child* OR adolescent* OR teen*)

ClinicalTrials.gov
Date Searched: 10/17/2016
Number of Results: 8

Search Terms: “mechanical ventilation” OR “artificial respiration”

Interventions: “deep sedation” OR “conscious sedation” OR “light sedation”

Outcome Measures: delirium OR “length of stay” OR extubation OR tracheostomy

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page Number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1,5
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	9
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	9
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4,5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplement 2
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5, 6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5,6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5,6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	6,7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Secondary Subject Heading:	Emergency medicine, Anaesthesia
Keywords:	Sedation, Mechanical Ventilation, Systematic Review, Meta-analysis, Protocol

TITLE: Practice patterns and outcomes associated with early sedation depth in mechanically ventilated patients: a systematic review protocol

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ABSTRACT

Introduction: Mechanical ventilation is a commonly performed intervention in critically ill patients. Frequently, these patients experience deep sedation early in their clinical course. Emerging data suggest that the practice of early deep sedation may negatively impact patient outcomes. The purpose of this review is to assess the world's literature to describe and determine the impact of early deep sedation on the outcomes of mechanically ventilated patients.

Methods and analysis: Randomized controlled trials and non-randomized studies will be eligible for inclusion in this systematic review. With the assistance of a medical librarian, we will comprehensively search MEDLINE, EMBASE, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews and Effects (DARE), and Cochrane Database of Systematic Reviews for peer reviewed literature. Grey literature from appropriate professional society conferences, held from 2010 to 2017, will be reviewed manually. Two authors will independently review all search results and disagreements will be resolved through arbitration by a third author. If appropriate, meta-analysis will be used for quantitative analysis of the data. Heterogeneity between studies will be assessed using the I^2 statistic.

Ethics and dissemination: The proposed systematic review will not collect data that is associated with individual patients and does not require ethical approval. Results of this study will contribute to the understanding of early sedation, identify future research targets, and guide early care in mechanically ventilated patients.

Study registration number: This systematic review has been registered in the PROSPERO international prospective register of systematic reviews (#CRD42017057264).

ARTICLE SUMMARY

Strengths and Limitations

- This is the first systematic review specifically studying the impact of early sedation depth on patient important outcomes
- In preparation of this protocol we followed the PRISMA-P guidelines and our study is registered with the PROSPERO international prospective register of systematic reviews.
- Our robust search strategy will decrease our risk of missing relevant studies.
- Our inclusion of non-randomized trials increases the risk of study bias.

Keywords: Sedation, Mechanical ventilation, Systematic Review, Meta-analysis

TEXT

INTRODUCTION

Mechanically ventilation is a common intervention in critically ill patients[1]. There is increasing recognition that the management of non-ventilator related aspects of care is highly influential on outcome. The management of sedation plays a major role in the care of mechanically ventilated patients[2]. While necessary to relieve pain and anxiety and improve tolerance of mechanical ventilation, sedatives have adverse effects on important patient-centered outcomes, such as lengths of stay, delirium, and mortality[3 4]. Present guidelines recommend that sedatives be titrated to achieve light, as opposed to deep, levels of sedation[2].

Despite these recommendations, deep sedation in the intensive care unit (ICU) is common. Specifically, early deep sedation (i.e. during the first 48 hours following initiation of mechanical ventilation) occurs in up to 76% of patients[5 6]. An emerging body of research suggests that the level of sedation during this early time period is an independent predictor of patient outcomes[7 8]. However, the bulk of prior sedation research has not been devoted to this initial early period, often not enrolling patients until after 48 hours of mechanical ventilation[6].

While the available evidence supports maintenance of early light sedation, the strength of the association remains unclear.

There have been no systematic reviews on the impact of early sedation on clinical outcomes. An important next step for investigating early sedation practices is to analyze the world literature to ascertain the true impact of early sedation. In this systematic review, we seek to 1) describe the state of global literature focusing on early sedation; and 2) quantify the impact of early sedation depth on patient-centered outcomes. We hypothesize that deep sedation in the 48 hour period follow initiation of mechanical ventilation will be associated with increased mortality and longer lengths of stay.

METHODS AND ANALYSIS

Protocol and registration

This systematic review protocol is prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement (online supplementary additional file 1)[9 10]. The final results will be reported according to PRISMA and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines[11 12]. Any deviation from the protocol will be reported with the final results, along with a rationale for protocol deviation. This study will be conducted starting in February 2017 with an intended completion date in May 2017. This systematic review has been registered in the PROSPERO international prospective register of systematic reviews (#CRD42017057264).

Search for and identification of studies

An electronic search will include the following databases: MEDLINE, EMBASE, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews and Effects (DARE), and Cochrane Database of Systematic Reviews. The search terms include the concepts of mechanical ventilation, sedation depth, critical illness, and outcome measures (including delirium, mortality, length of stay, tracheostomy, time to extubation, and time ventilated). These strategies were established using a combination of standardized terms and

key words. The fully reproducible search strategy is provided in the online supplementary additional file 2. The search was designed in cooperation with a medical librarian, who performed the electronic search.

The reference lists of the articles selected for inclusion will be manually screened to identify additional studies. To identify potential unpublished data, abstracts from the following meetings (from 2010 to 2017) will be manually searched: Society of Critical Care Medicine, European Society of Intensive Care Medicine, International Symposium on Intensive Care and Emergency Medicine, American Thoracic Society, Society for Academic Emergency Medicine, Pharmacotherapy, American Society of Anesthesiologists, European Society of Anaesthesiology, International Anesthesia Research Society, Trauma, Critical Care & Acute Care Surgery, American Association for the Surgery of Trauma, and the Eastern Association for the Surgery of Trauma. An online search for details of clinical trials registration (ClinicalTrials.gov) will also be conducted to identify completed, but not yet published, clinical studies. The principal investigators of published and unpublished studies will also be contacted as needed for clarification of potential data for inclusion.

Eligibility criteria

Studies will be eligible regardless of language, and will include adult patients receiving invasive positive pressure ventilation. Randomized controlled trials (RCT), as well as non-randomized studies (prospective and retrospective cohort analyses, cross-sectional studies, before-after trials) will be included. Non-randomized studies will be included for the following reasons: 1) a likelihood that the question of interest may not be investigated strictly with RCTs secondary to a lack of existing randomized trials; 2) to provide an explicit evaluation of strengths and weaknesses of the current literature; 3) to assess evidence of effects (benefit and harm); and 4) to provide evidence for the undertaking of randomized trials. Papers that are reviews, correspondences, editorials, and non-human studies will be excluded. Eligibility criteria are listed in Table 1.

The intervention will be the sedation provided during the first 48 hours of mechanical ventilation. The comparison will be sedation depth (light sedation versus deep sedation). Eligible studies must report some objective measure of sedation depth, such as the Richmond Agitation-Sedation Scale (RASS) or the Glasgow Coma Scale (GCS). The clinical outcomes will be assessed according to sedation depth. These include: mortality, delirium, ventilator-free days, hospital and ICU lengths of stay, and incidence of tracheostomy. The drugs used for early sedation will also be qualitatively reported, as will the study location (i.e. ICU, emergency department). If there is a relative paucity of data describing early sedation, we will also qualitatively report the sedation provided at trial enrollment for RCTs. Similarly, we will report the depth of sedation at the time of trial enrollment for RCTs.

Study selection and data abstraction

Two independent reviewers will screen titles and abstracts of identified studies for eligibility. After this relevance screen, the two reviewers will compare their included studies to determine if disagreement exists. In cases of disagreement, the opinion of a third reviewer will be sought and a consensus will be reached. Full text articles will then be obtained and these manuscripts will be reviewed for potential inclusion.

The same two reviewers will extract data using standardized forms. The following data on study characteristics will be collected and placed in a table: author, year of publication, study design, number of patients included, characteristics of the patient population, sedation data, study quality, risk of bias, and outcomes. We will include pertinent study-specific comments in the table as needed.

Assessment of study quality

We will assess quality of randomized clinical trials using the Cochrane Collaboration's tool for assessing the risk of bias in clinical trials and report a summary assessment for the risk of bias for each studied outcome[13]. For studies of observational design, quality will be assessed

with the Newcastle Ottawa Scale, assigning a maximum of nine points. Five or fewer points will indicate a high risk of bias[14].

Assessment of publication bias

A graphical display (funnel plot) of the size of the treatment effect against the precision of the trial will be used to evaluate for potential publication bias.

Strategy for data synthesis

We will provide a comprehensive narrative synthesis and qualitative analysis of the data, structured around outcomes related to sedation. After conducting the systematic review, if the data can be pooled, we will use a meta-analytic approach to quantitatively analyze the data. A random effects model will be used to calculate pooled effect sizes and corresponding 95% confidence intervals [CI] between deep and light sedation groups. Odds ratios will be calculated for binary data, such as mortality comparisons. Continuous outcomes will be reported as mean difference, and overall effect estimates will be generated using a Z test and presented as mean differences. A p value of < 0.05 will be considered statistically significant.

Heterogeneity between studies will be assessed using the I^2 statistic, which will be reported as a point estimate with 95% confidence intervals. We will interpret this statistic using suggested thresholds for low (25-49%), moderate (50-74%), and high (≥75%) values[15].

We will perform sensitivity and subgroup analyses if the systematic review suggests that this is feasible and warranted to explore heterogeneity between studies.

ETHICS AND DISSEMINATION

As this is a systematic review of completed studies, no ethical approval will be required. Results from this systematic review will be submitted for publication in peer-reviewed journals, and will be presented at national meetings.

This study will refine the understanding of the impact of early sedation practices and inform healthcare workers providing care to mechanically ventilated patients. We anticipate that

this information will improve the post-intubation care received by mechanically ventilated patients.

Over the past decade, there has been an increasing recognition that early advanced care has significant impact on patient outcome during critical illness. This concept has been shown to be true with regard to antibiotics in sepsis, lung protective ventilation in respiratory failure, and reperfusion therapy in cerebrovascular accident[16-19]. However, there has not been a similar focus on early sedation care for patients treated with mechanical ventilation.

This systematic review will provide a complete synopsis of the world's literature examining the impact of early deep sedation on patient outcomes, including mortality and lengths of stay. We will assess the cohort of studies for study quality, publication bias, heterogeneity, and determine if a meta-analysis is appropriate. We expect to find that early deep sedation is associated with worse mortality, longer lengths of stay, and greater ventilation duration. Furthermore, we will identify knowledge gaps in the literature as future research targets.

In conclusion, this systemic review will aim to characterize and quantify the impact of early sedation on patient important outcomes. We hope this study yields additional evidence to guide clinical practice in mechanically ventilated patients, as well as targets for future investigation.

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AUTHOR CONTRIBUTIONS:
RJS: Study conception and design, drafting the manuscript, critical revision, guarantor of the review
MRD: Drafting the manuscript, critical revision

BWR: Study design, drafting the manuscript, critical revision
SAF: Study design, devising the search strategy
BMF: Study conception and design, drafting the manuscript, critical revision

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BMF was funded by the KL2 Career Development Award, and this research was supported by Washington University Institute of Clinical and Translational Sciences (GRANTS UL1 TR000448 and KL2 TR000450) from the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (NIH). BMF was also funded by the Foundation for Barnes-Jewish Hospital Clinical and Translational Sciences Research Program (Grant # 8041-88). BWR was supported by a grant from the National Institutes of Health/National Heart, Lung, and Blood Institute (K23HL126979).

COMPETING INTERESTS STATEMENT:
All authors declare that they have no significant competing financial, professional, or personal interests that may influence the performance or presentation of this study.

Table 1. Eligibility criteria for inclusion in systematic review

	Inclusion Criteria	Exclusion Criteria
Population	• Age ≥ 18 years	• Age < 18 years
Intervention	• Invasive positive pressure ventilation	• Chronic ventilation
Reference Standard	• Objective measure of sedation depth	• None
Outcomes	• Mortality • Hospital length of stay • ICU length of stay • Time to extubation • Delirium • Incidence of tracheostomy	• None
Study Design	• Randomized controlled trials • Prospective cohort studies • Retrospective cohort studies • Cross-sectional studies • Before-after trials	• Correspondences • Editorials • Non-human studies

Prepared by:

Susan A. Fowler, MLIS
Bernard Becker Medical Library
Washington University in St. Louis

Methods section text:

The published literature was searched using strategies created by a medical librarian for the concepts of mechanical ventilation, sedation depth, critical illness, and outcome measures including delirium, mortality, length of stay, tracheostomy, time to extubation, and time ventilated. These strategies were established using a combination of standardized terms and key words. To exclude animals, SF used the Human filter for Medline recommended in Cochrane Handbook for Systematic Reviews of Interventions and modified it to create similar filters for the other databases searched. Database platforms searched include Ovid Medline 1946-, Embase.com 1947-, Scopus.com 1823-, Wiley Cochrane Central Register of Controlled Trials (CENTRAL), Wiley Database of Abstracts of Reviews of Effects (DARE), and Wiley Cochrane Database of Systematic Reviews. All searches were completed in October 2016. All results were exported to EndNote. We used the automatic duplicate finder in EndNote and hand searched for duplicates as well to accurately identify and remove duplicates resulting in a total of 946 unique citations. Clinicaltrials.gov was also searched with a total of 8 resulting trials. Full search strategies are provided.

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

Search Strategies

Ovid Medline
Date Searched: 10/11/2016
Applied Database Supplied Limits: 0
Number of Results: 446

Full Search Strategy:

(exp Respiration, Artificial/ OR (Respironics V60 OR Servo-I OR Tangens 2C).mp. OR ((mechanical* OR artificial*) ADJ2 (ventilat* OR respirat*).mp.) OR (ventilat* adj8 patient*).mp.) AND (exp Critical Illness/ OR Critical Care/ OR exp Intensive Care Units/ OR Emergencies/ OR exp Emergency Service, Hospital/ OR Emergency Medicine/ OR (critical* adj3 ill*).mp. OR ((intensive OR subacute OR critical) adj3 (care OR therap*)).mp. OR emergenc*.mp. OR ((accident OR trauma OR urgent) adj2 (service* OR center* OR centre* OR dispensary)).mp.) AND (exp Deep Sedation/ OR exp Conscious Sedation/ OR ((moderate OR conscious OR light* OR deep OR depth* OR level*) ADJ3 sedat*).mp.) AND (exp Delirium/ OR exp Mortality/ OR exp "Length of Stay"/ OR exp Tracheostomy/ OR (delirium* OR delirious OR delire OR delier OR mortal* OR death* OR died OR fatal* OR Tracheostom*).mp. OR ((length OR time OR day* OR hospital OR unit) adj5 (stay* OR discharge* OR duration)).mp. OR ((time* OR delay*) adj2 (extubat*)).mp. OR ((prolong* OR duration OR day*) adj5 (ventilat*)).mp.) not ((exp Animals/) not (exp Animals/ and exp Humans/))

Embase
Date Searched: 10/11/2016
Applied Database Supplied Limits: 0
Number of Results: 608

Full Search Strategy:

('mechanical ventilator'/exp OR 'artificial ventilation'/exp OR 'Respironics V60' OR 'Servo-I' OR 'Tangens 2C' OR 'ventilated patient'/exp OR (mechanical* OR artificial*) NEAR/2 (ventilat* OR respirat*) OR (ventilat* NEAR/8 patient*)) AND ('critically ill patient'/exp OR 'intensive care'/de OR 'emergency health service'/exp OR 'emergency ward'/exp OR 'emergency'/exp OR 'emergency medicine'/exp OR critical* NEAR/3 ill* OR (intensive OR subacute OR critical) NEAR/3 (care OR therap*) OR emergenc* OR (accident OR trauma OR urgent) NEAR/2 (service* OR center* OR centre* OR dispensary)) AND ('conscious sedation'/exp OR 'deep sedation'/exp OR (moderate OR conscious OR light* OR deep OR depth* OR level*) NEAR/3 sedat*) AND ('delirium'/exp OR 'mortality'/exp OR 'length of stay'/exp OR 'hospital discharge'/exp OR 'tracheostomy'/exp OR delirium* OR delirious OR delire OR delier OR mortal* OR death* OR died OR fatal* OR Tracheostom* OR (length OR time OR days OR hospital OR unit) NEAR/5 (stay* OR discharge* OR duration) OR (time* OR delay*) NEAR/2 extubat* OR (prolong* OR duration OR day*) NEAR/5 ventilat*) NOT ([animals]/lim NOT [humans]/lim)

Cochrane
Date Searched: 10/17/2016
Applied Database Supplied Limits: 0
Number of Results from each database in Cochrane
CDSR: 39
CENTRAL: 116
DARE: 6

Full Search Strategy:

([mh "Respiration, Artificial"] OR 'Respironics V60' OR 'Servo-I' OR 'Tangens 2C' OR ((mechanical* OR artificial*) NEAR/2 (ventilat* OR respirat*)) OR (ventilat* NEAR/8 patient*)) AND ([mh "Critical Illness"] OR [mh ^"Critical Care"] OR [mh "Intensive Care Units"] OR [mh ^"Emergencies"] OR [mh "Emergency Service, Hospital"] OR [mh "Emergency Medicine"] OR (critical* NEAR/3 ill*) OR ((intensive OR subacute OR critical) NEAR/3 (care OR therap*)) OR emergenc* OR ((accident OR trauma OR urgent) NEAR/2 (service* OR center* OR centre* OR dispensary))) AND ([mh "Deep Sedation"] OR [mh "Conscious Sedation"] OR ((moderate OR conscious OR light* OR deep OR depth* OR level*) NEAR/3 (sedat*))) AND ([mh "Delirium"] OR [mh "Mortality"] OR [mh "Length of Stay"] OR [mh "Tracheostomy"] OR delirium* OR delirious OR delire OR delier OR mortal* OR death* OR died OR fatal* OR ((length OR time OR days OR hospital OR unit) NEAR/5 (stay* OR discharge* OR duration)) OR Tracheostom* OR

((time* OR delay*) NEAR/2 (extubat*)) OR ((prolong* OR duration OR day*) NEAR/5 (ventilat*))) NOT (([mh “Animals”]) NOT ([mh “Animals”] AND [mh “Humans”]))

Scopus
Date Searched: 10/17/2016
Applied Database Supplied Limits: 0
Number of Results: 591

Full Search Strategy:

(TITLE-ABS-KEY("Respironics V60" OR "Servo-I" OR "Tangens 2C") OR TITLE-ABS-KEY((mechanical* OR artificial*) W/2 (ventilat* OR respirat*)) OR TITLE-ABS-KEY(ventilat* W/8 patient*)) AND (TITLE-ABS-KEY(critical* W/3 ill*) OR TITLE-ABS-KEY((intensive OR subacute OR critical) W/3 (care OR therap*)) OR TITLE-ABS-KEY(emergenc*) OR TITLE-ABS-KEY((accident OR trauma OR urgent) W/2 (service* OR center* OR centre* OR dispensary))) AND (TITLE-ABS-KEY((moderate OR conscious OR light* OR deep OR depth* OR level*) W/3 (sedat*))) AND (TITLE-ABS-KEY(delirium* OR delirious OR delire OR delier OR mortal* OR death* OR died OR fatal*) OR TITLE-ABS-KEY((length OR time OR days OR hospital OR unit) W/5 (stay* OR discharge* OR duration)) OR TITLE-ABS-KEY(Tracheostom*) OR TITLE-ABS-KEY((time* OR delay*) W/2 (extubat*)) OR TITLE-ABS-KEY ((prolong* OR duration OR day*) W/5 (ventilat*))) AND KEY(human OR humans OR woman OR man OR women OR men OR child* OR adolescent* OR teen*)

ClinicalTrials.gov
Date Searched: 10/17/2016
Number of Results: 8

Search Terms: “mechanical ventilation” OR “artificial respiration”

Interventions: “deep sedation” OR “conscious sedation” OR “light sedation”

Outcome Measures: delirium OR “length of stay” OR extubation OR tracheostomy

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page Number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1,5
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	9
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	9
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4,5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplement 2
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5, 6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5,6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5,6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	6,7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.