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Skeletal Muscle Relaxants as Adjunctive Pain control following Cardiothoracic Surgery - Systematic Review Protocol

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Abstract

Introduction

Multimodal pain control following cardiothoracic surgery remains a focus in international guidelines. We hypothesize that non-depolarizing skeletal muscle relaxants can prove to be a useful adjunct for this population.

Methods/analysis

This systematic review will focus on human adult studies of pain control using muscle relaxants following cardiac and thoracic surgery available in PubMed, Web of Science and EMBASE. Target studies will have a primary focus on measured effects on quality of pain control and reduction in opioid usage. Studies that include non-depolarizing skeletal muscle relaxants given during or after cardiothoracic surgery will be included. Study selection will be in keeping with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. If sufficient data involving a given agent are available, a meta-analysis will be conducted and compared to current evidence for therapies recommended in international practice guidelines.

Ethics and dissemination

Formal ethical approval will not be required as primary data will not be collected. The results will be disseminated through peer-reviewed publication, conference presentation and lay press.

Prospero registration number: International Prospective Register for Systematic Reviews (PROSPERO) number CRD42023397917

Article Summary

Strengths and limitations of this study

- Systematic review and meta-analysis of studies examining the effects of non-paralytic skeletal muscle relaxants following cardiothoracic surgery.
- Focus on a class of medications that is potentially underutilized based on current guidelines.
- Limitation in the number of studies investigating a given therapy may diminish observed effects.
- Potential identification of therapies with positive impact on pain control following cardiothoracic surgery.

Introduction

Postoperative pain after thoracic surgery can be severe and attributed to a constellation of factors including rib retraction, sternal fracture, prolonged immobility, intercostal nerve stimulation, and pleural irritation from chest tubes. Per current recommendations by the Enhanced Recovery After Surgery Society (ERAS) and the European Society of Thoracic Surgeons (ESTS), a consistent multimodal analgesic approach is essential to patient comfort, early mobility, avoidance of opioids, and reduced likelihood of pulmonary complications following thoracic and cardiac surgery (1). These guidelines recommend regional anesthesia, scheduled administration of acetaminophen and NSAIDs, ketamine, and dexamethasone. Gabapentinoids also feature heavily in common multimodal anesthetic pathways despite data suggesting limited effects following cardiothoracic procedures (2). Additionally, these guidelines may not provide sufficient guidance for patients with underlying liver or kidney disease, making it important to explore alternative options such as muscle relaxants.

Muscle relaxants as a class are commonly used to treat spasticity and musculoskeletal disorders, with well-documented effectiveness in chronic spastic musculoskeletal pain, multiple sclerosis, and spinal cord injuries (3, 4). Baclofen, tizanidine, and dantrolene are approved to treat spasticity, though baclofen withdrawal can be life-threateningly severe (5). Baclofen and tizanidine are centrally acting and block $GABA_B$ receptors found in the spinal cord or brainstem (6, 7), while dantrolene directly inhibits muscle contraction by reducing the release of calcium from the skeletal muscle sarcoplasmic reticulum (8). More pertinent to post-operative pain, agents such as carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, and orphenadrine are approved for the treatment of musculoskeletal disorders (5). While used in the treatment of acute injuries, we hypothesize that there may be a role for use following cardiothoracic surgery.

This review aims to summarize the current literature on the effectiveness of non-paralytic muscle relaxants in postoperative pain management for cardiac and thoracic surgery patients. The aim is to provide and evidence basis for alternative analgesics beyond those offered by current guidelines.

PROSPERO ID: CRD42023397917

Objectives

The objective of our study is to systematically review the literature for the use of non-paralytic skeletal muscle relaxants as adjuncts for non-opioid pain control following cardiac or thoracic surgery. This will include all human adult studies available in the literature for post-operative pain control.

Methods and Design

Population

The systematic review will focus on studies that include patients aged >18 years who have undergone cardiac or thoracic surgery.

Interventions

The interventions to be evaluated include any non-paralyzing muscle relaxant as part of a pain control regimen for cardiac or thoracic surgery. This includes centrally acting muscle relaxants such as cyclobenzaprine and methocarbamol as well as antispastics and antispasmodics such as baclofen. This specifically excludes studies evaluating the role of paralytics in pain control.

Comparisons

The quantifiable benefits and side effects of the interventions identified will be compared to current practice guidelines and the pharmacologic agents advocated therein, specifically gabapentinoids and opioids.

Outcome

The primary outcomes required of included studies will be one of the following: qualitative and quantitative assessment for pain control, either through patient satisfaction visual analog scale or numeric rating scheme, days of pain control, time to pain control, or measures of effect on functional status. Additional outcome measures may include sedation or other side effects, and comparison in opioid usage. Secondary outcomes will also include effect on length of stay, incidence of falls, anticholinergic side effects and withdrawal episodes upon removal of muscle relaxant.

Study Design

The systematic review and meta-analysis will include all therapeutic studies investigating the use of a non-paralyzing muscle relaxant for pain control following cardiac or thoracic surgery. This will include systematic reviews, meta-analyses, randomized control trials, adaptive clinical trials, prospective cohort and observational studies, non-randomized clinical trials, retrospective cohorts, case control studies, case reports, and case series. Studies that compare one intervention to usual practices recommended by ERAS/ ESTS as the control will be included. No minimum number of included subjects will be required. The review will exclude studies without a control group using either placebo or current standard care. Excluded study types include cross sectional studies, editorials, preclinical or animal models, and studies in the outpatient setting. This review has been registered on the International Prospective Register for Systematic Reviews (PROSPERO) number CRD42023397917.

Search Strategy

A three-step process will be used to identify eligible studies, including an initial search, title and abstract screening and full-text manuscript review. A professional systematic review librarian will provide guidance in developing the search criteria with the authors to include all relevant studies pertaining to adult, human studies non-paralyzing muscle relaxants for pain control after thoracic and cardiac surgery. The databases that will be searched are PubMed, Web of Science and EMBASE from inception. No language restrictions will be applied. Figure 1 shows an example search algorithm for PubMed. Initial deduplication will be performed using EndNote (Clarivate Analytics, Philadelphia, Pennsylvania, USA).[10]

Study Selection

Literature search results will be uploaded from EndNote and screened through Covidence (*Melbourne, Victoria, Australia*). Study titles and abstracts will be screened for relevance in duplicate, blindly and independently, by the three junior authors (SK, QW, and MF) and adjudicated by the senior author (TM). Eligible studies will then be assessed again for inclusion and for quality in secondary screening through review of full-text manuscripts before data abstraction. This process will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. The PRISMA-P Checklist pertaining to this protocol is available as Supplement 1. Any conflicting remarks regarding studies will be adjudicated through discussion before inclusion in the final analysis.

Quality Assessment

Each article will undergo initial title and abstract screening in parallel by two independent, blinded reviewers to minimize bias. Conflicts will be adjudicated with discussion and involvement of the senior

author as necessary. All selected articles will be reviewed with the senior author during full-text review. Cochrane tools for assessment of study quality (ROBINS-1 and RoB 2.0) will be used to determine appropriateness for inclusion. Two independent authors, one being the senior author, will assess the risks of bias in studies considered for full-text review in order to determine feasibility of a meta-analysis.

Data Extraction

Quantitative data will be extracted from studies meeting inclusion upon full-text review by a professional biostatistician. Data extracted for meta-analysis will be specifically those pertinent to the primary and secondary outcomes specified in the systematic review. This will include demographics of patient populations, types of surgical procedures performed, medications administered, and outcome parameters as well as any data that are available across all included studies. Data extraction will be independently cross-checked by the senior author and discrepancies resolved through discussion with the biostatistician. The raw data for this review including a dataset of articles screened will be published in a data repository.

Endpoint

Results of the systematic review will be grouped by drug. The primary outcomes will be quality of pain control as measured by patient satisfaction scores, visual analog scale, numeric ratings, days of pain control reported, intensity of pain reported, timing to effective pain control, sedating side effects, seizures or other adverse effects, effect on functional mobility and effect on opioid requirements. We will also include secondary outcomes of effect on length of stay, incidence of falls or injury due to muscle relaxants, anticholinergic reactions, withdrawal events upon cessation. Any follow-up duration will be accepted as there is considerable variability in the existing literature.

Patient and Public Involvement

No patients were involved with the planning of this protocol.

Analysis

Descriptive Analysis

A narrative synthesis of the final studies included will be written summarizing the different non-paralyzing muscle relaxants identified. The impact of each of these agents on the primary and secondary outcomes will be described in addition to a formal meta-analysis of studies using each pharmacologic agent if sufficient studies are available for a given agent.

Statistical Analysis

The primary focus of this review is to detect evidence for the impact of the pharmacologic agents identified on pain control and opioid usage. 'Pain control' is quantified in different ways that are important to patients including intensity, days of control, improvement from prior pain and whether pain limits functional mobility. As the effects of non-paralyzing muscle relaxants are studies differently, we expect some limitation in the ability to directly compare one agent to standard protocols or to one another. However, when available, pharmacologic agents will be compared as equitably as possible using all available outcome parameters reported in the primary literature. If sufficient data from primary sources is available, subgroup analysis within populations of similar operations and treated with the same pharmacologic agents will also be performed to identify populations most likely to benefit from a given agent.

Data synthesis

A PRISMA flow diagram will be used to summarize study selection. Results will be presented in accordance with the PRISMA statement. Tabulated data showing qualitative and quantitative pain control for each pharmacologic agent and surgical intervention will be presented. For secondary outcome variables, we will present synthesized data as available in separate tables but will otherwise provide a separate narrative summary of the data available for each agent. We will produce a hierarchy of pharmacologic agents for each surgical type (cardiac or thoracic) based on the quality of evidence available and degree of effects on outcome variables.

Meta-analysis

A meta-analysis of the pharmacologic agents will be performed as able based on availability of primary data. The results of this meta-analysis will then be compared to current ERAS and ESTS practice guidelines to provide context and compare relative efficacy.

Discussion

This systematic review and meta-analysis will provide evidence for further use or study of non-paralyzing muscle relaxants as analgesic adjuncts in patients following cardiac or thoracic surgery. The conclusions will be the result of careful accumulation of the highest-quality evidence available and will compare to current practice guidelines to provide clinical context. With a primary focus on the ability of a given medication to improve pain control with a favorable side effect profile while minimizing exposure to opioids, this review and meta-analysis will be unique in identifying agents with the greatest potential.

Ethics and dissemination

No ethical or safety considerations were considered based on the nature of this review. Dissemination of findings through a peer-reviewed publication upon the conclusion of the meta-analysis.

Author Contributions

Travis Murphy: Conception and design of work, analysis, drafting of work, final approval *Shadman Kabir:* Conception of work, analysis, drafting of work, final approval *Quinn Whaley:* Analysis, drafting of work, final approval *Melissa Fernandez:* Analysis, drafting of work, final approval

Funding statement

This project did not receive any internal or external funding.

Competing interest statement

The authors have no competing interests.

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Figure 1. Example Search Algorithm for PubMed

PubMed Search String

Cardiothoracic Surgery:

("Cardiovascular Surgical Procedures"[MeSH Terms] OR "surgical procedures, operative"[MeSH Terms] OR "Perioperative Care"[MeSH Terms] OR "Thoracic Surgical Procedures"[MeSH Terms])

Results 1: ***3,501,498***

AND

Muscle Relaxants:

("centrally acting muscle relaxant"[All Fields] OR "muscle relaxant"[All Fields] OR "methocarbamol"[All Fields] OR "cyclobenzaprine"[All Fields] OR "baclofen"[All Fields] OR "skeletal muscle relaxant"[All Fields] OR "tizanidine"[All Fields] OR "carisoprodol"[All Fields] OR "metaxalone"[All Fields] OR "orphenadrine"[All Fields] OR "chlorzoxazone"[All Fields] OR "dantrolene"[All Fields])

Results 2: ***18,392***

Combined Results 1+2: ***1,532***

Date: April 18, 2023

Figure 1. PubMed Search String

Cardiothoracic Surgery:

("Cardiovascular Surgical Procedures"[MeSH Terms] OR "surgical procedures, operative"[MeSH Terms] OR "Perioperative Care"[MeSH Terms] OR "Thoracic Surgical Procedures"[MeSH Terms])

Results 1: ***3,501,498***

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Muscle Relaxants:

("centrally acting muscle relaxant"[All Fields] OR "muscle relaxant"[All Fields] OR "methocarbamol"[All Fields] OR "cyclobenzaprine"[All Fields] OR "baclofen"[All Fields] OR "skeletal muscle relaxant"[All Fields] OR "tizanidine"[All Fields] OR "carisoprodol"[All Fields] OR "metaxalone"[All Fields] OR "orphenadrine"[All Fields] OR "chlorzoxazone"[All Fields] OR "dantrolene"[All Fields])

Results 2: ***18,388***

Combined Results 1+2: ***1,529***

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	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	P.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	P.2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	P.1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	P.6
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	P.6
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	N/a
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	P.3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	P.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	P.3
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	P.4
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	P.8

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	P.4
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)	P.4
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	P.5
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	P.4
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	P.4
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	P.6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	P.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)	P.6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	P.6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	P.7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	P.5

*** 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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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Surgery, Pharmacology and therapeutics, Intensive care, Anaesthesia, Cardiovascular medicine
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Introduction

Multimodal pain control following cardiothoracic surgery remains a focus in international guidelines. We hypothesize that non-depolarizing skeletal muscle relaxants can prove to be a useful adjunct for this population.

Methods/analysis

This systematic review will focus on human adult studies of pain control using muscle relaxants within one week following cardiac and thoracic surgery available in PubMed, Cochrane Central, Web of Science and EMBASE. Target studies will have a primary focus on measured effects on quality of pain control and reduction in opioid usage. Studies that include non-depolarizing skeletal muscle relaxants given during cardiothoracic surgery or in the week after will be included. Study selection will be in keeping with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Procedures and agents used will be analyzed together, and a meta-analysis will be conducted then compared to current therapies recommended in international practice guidelines.

Ethics and dissemination

Formal ethical approval will not be required as primary data will not be collected. The results will be disseminated through peer-reviewed publication, conference presentation and lay press.

Prospero registration number: International Prospective Register for Systematic Reviews (PROSPERO) number CRD42023397917

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- Systematic review and meta-analysis of studies examining the effects of non-paralytic skeletal muscle relaxants following cardiothoracic surgery.
- Focus on a class of medications that is potentially underutilized based on current guidelines.
- Limitation in the number of studies investigating a given therapy may diminish observed effects.
- Potential identification of therapies with positive impact on pain control following cardiothoracic surgery.

Introduction

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This review aims to summarize the current literature on the effectiveness of non-paralytic muscle relaxants in postoperative pain management for cardiac and thoracic surgery patients. The aim is to provide and evidence basis for alternative analgesics beyond those offered by current guidelines.

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Objectives

The objective of our study is to systematically review the literature for the use of non-paralytic skeletal muscle relaxants as adjuncts for non-opioid pain control following cardiac or thoracic surgery. This will include all human adult studies available in the literature for post-operative pain control.

Methods and Design

Population

The systematic review will focus on studies that include patients aged >18 years who have undergone cardiac or thoracic surgery.

Interventions

The interventions to be evaluated include any non-paralyzing muscle relaxant as part of a pain control regimen for cardiac or thoracic surgery. This includes centrally acting muscle relaxants such as cyclobenzaprine and methocarbamol as well as antispastics and antispasmodics such as baclofen. This specifically excludes studies evaluating the role of paralytics in pain control.

Comparisons

We will compare adult patients undergoing cardiac and thoracic surgery and receiving standard multimodal analgesia (acetaminophen, gabapentin, and others) with those receiving non-depolarizing skeletal muscle relaxants.

Outcome

The primary outcomes required of included studies will be one of the following: qualitative and quantitative assessment for pain control, either through patient satisfaction visual analog scale or numeric rating scheme, days of pain control, time to pain control, or measures of effect on functional status. Additional outcome measures may include sedation or other side effects, and comparison in opioid usage. Secondary outcomes will also include effect on length of stay, incidence of falls, anticholinergic side effects and withdrawal episodes upon removal of muscle relaxant in addition to any other reported adverse events.

Time

The outlined outcomes will be reported from the post-operative phase through to hospital discharge.

Study Design

The systematic review and meta-analysis will include all therapeutic studies investigating the use of a non-paralyzing muscle relaxant for pain control following cardiac or thoracic surgery within a week of surgery and following outcomes up until hospital discharge. This will include systematic reviews, meta-analyses, randomized control trials, adaptive clinical trials, prospective cohort and observational studies, non-randomized clinical trials, retrospective cohorts, case control studies, case reports, and case series. Studies that compare one intervention to usual practices recommended by ERAS as the control will be included. No minimum number of included subjects will be required. The review will exclude studies without a control group using either placebo or current standard care. Excluded study types include cross sectional studies, editorials, preclinical or animal models, and studies in the outpatient setting. Finally, grey literature shall be omitted from consideration. This review has been registered on the International Prospective Register for Systematic Reviews (PROSPERO) number CRD42023397917.

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Checklist pertaining to this protocol is available as Supplement 1. Any conflicting remarks regarding studies will be adjudicated through discussion before inclusion in the final analysis.

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Quantitative data will be extracted from studies meeting inclusion upon full-text review by a professional biostatistician. Data extracted for meta-analysis will be specifically those pertinent to the primary and secondary outcomes specified in the systematic review. This will include demographics of patient populations, types of surgical procedures performed, medications administered, and outcome parameters as well as any data that are available across all included studies. Data extraction will be independently cross-checked by the senior author and discrepancies resolved through discussion with the biostatistician. The raw data for this review including a dataset of articles screened will be published in a data repository.

Endpoint

Results of the systematic review will be grouped by pharmacologic agent. The primary outcomes will be quality of pain control as measured by patient satisfaction scores, visual analog scale, numeric ratings, days of pain control reported, intensity of pain reported, timing to effective pain control, sedating side effects, seizures or other adverse effects, effect on functional mobility and effect on opioid requirements. We will also include secondary outcomes of effect on length of stay, incidence of falls or injury due to muscle relaxants, anticholinergic reactions, withdrawal events upon cessation. Any follow-up duration will be accepted as there is considerable variability in the existing literature.

Certainty of Cumulative Evidence

We will assess the certainty of evidence for each outcome using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework in reporting the endpoints discussed above. As there may not be sufficient data for a meta-analysis, the overall certainty will be communicated using the narrative statements recommended by the framework.

Patient and Public Involvement

No patients were involved with the planning of this protocol.

Analysis

Descriptive Analysis

A narrative synthesis of the final studies included will be written summarizing the different non-paralyzing muscle relaxants identified. The impact of each of these agents on the primary and secondary outcomes will be described in addition to a formal meta-analysis of studies using each pharmacologic agent. Included studies will be evaluated for statistical heterogeneity before formal analysis.

Statistical Analysis

The primary focus of this review is to detect evidence for the impact of the pharmacologic agents identified on pain control and opioid usage. 'Pain control' is quantified in different ways that are important to patients including intensity, days of control, improvement from prior pain and whether pain limits functional mobility. As the effects of non-paralyzing muscle relaxants are studied differently, we expect some limitation in the ability to directly compare one agent to standard protocols or to one another. However, when available, pharmacologic agents will be compared as equitably as possible using all available outcome parameters reported in the primary literature. Subgroup analysis within populations of similar operations and treated with the same pharmacologic agents will be performed to identify populations most likely to benefit from a given agent. We will use the risk ratio with 95% confidence interval to express the effect estimate for dichotomous outcome and will express the effect estimate as mean difference with 95% confidence interval for continuous outcomes. Analysis of covariance (ANCOVA) will be utilized for comparing clusters treated with agents and procedures as the baseline characteristics of groups in different studies are likely to be different.

Data synthesis

A PRISMA flow diagram will be used to summarize study selection. Results will be presented in accordance with the PRISMA statement. Tabulated data showing qualitative and quantitative pain control for each pharmacologic agent and surgical intervention will be presented. For secondary outcome variables, we will present synthesized data as available in separate tables but will otherwise provide a separate narrative summary of the data available for each agent. We will cluster studies of each pharmacologic agent for each surgical type (cardiac or thoracic) based on the quality of evidence available and outcome variables included.

Meta-analysis

We anticipate clinical and methodological heterogeneity of the included studies and will plan for a qualitative synthesis of data in narrative form and to the extent possible, a quantitative synthesis of the pharmacologic agents. The results of this meta-analysis will then be compared to current ERAS practice guidelines to provide context and compare relative efficacy.

Ethics and dissemination

No ethical or safety considerations were considered based on the nature of this review. Dissemination of findings through a peer-reviewed publication upon the conclusion of the meta-analysis.

Author Contributions

Travis Murphy: Conception and design of work, analysis, drafting of work, final approval *Shadman Kabir:* Conception of work, analysis, drafting of work, final approval *Quinn Whaley:* Analysis, drafting of work, final approval *Melissa Fernandez:* Analysis, drafting of work, final approval

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Competing interest statement

The authors have no competing interests.

Figure 1. Example Search Algorithm for PubMed

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Figure 1. Example Search Algorithm for PubMed

PubMed Search String

(thoracic surgical procedures[MeSH Terms]) OR (cardiovascular surgery[Title/Abstract]) OR (thoracic surgery[Title/Abstract])

AND

(pain post operative[MeSH Terms]) OR (pain management[MeSH Terms]) OR (pain perception[MeSH Terms]) OR (pain measurement[MeSH Terms]) OR (length of stay[MeSH Terms]) OR (accidental falls[MeSH Terms]) OR (substance withdrawal syndrome[MeSH Terms]) OR (post operative pain[Title/Abstract]) OR (pain management[Title/Abstract]) OR (length of stay[Title/Abstract]) OR (hospital stay[Title/Abstract]) OR (accidental falls[Title/Abstract]) OR (pain perception[Title/Abstract]) OR (pain measurement[Title/Abstract]) OR (withdrawal[Title/Abstract])

AND

(muscle relaxants, central[MeSH Terms]) OR (methocarbamol[MeSH Terms]) OR (baclofen[MeSH Terms]) OR (carisoprodol[MeSH Terms]) OR (orphenadrine[MeSH Terms]) OR (Chlorzoxazone[MeSH Terms]) OR (dantrolene[MeSH Terms]) OR (analgesics[MeSH Terms]) OR (cyclobenzaprine[Supplementary Concept]) OR (tizanidine[Supplementary Concept]) OR (metaxalone[Supplementary Concept]) OR (orphenadrine[MeSH Terms]) OR (dantrolene[MeSH Terms]) OR (muscle relaxant[Title/Abstract]) OR (methocarbamol[Text Word]) OR (cyclobenzaprine[Text Word]) OR (baclofen[Text Word]) OR (tizanidine[Text Word]) OR (carisoprodol[Text Word]) OR (metaxalone[Text Word]) OR (orphenadrine[Text Word]) OR (chlorzoxazone[Text Word]) OR (dantrolene[Text Word]) OR (analgesics[Text Word])

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	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	P.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	P.2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	P.1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	P.6
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	P.6
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	N/a
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	P.3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	P.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	P.3
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	P.4
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	P.8

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	P.4
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)	P.4
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	P.5
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	P.4
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	P.4
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	P.6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	P.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)	P.6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	P.6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	P.7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	P.5

*** 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.**

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