COMPARING PRETREATMENT MODALITIES FOR THE PREVENTION OF SUCCINYLCHOLINE-INDUCED FASCICULATIONS IN ADULTS UNDERGOING ENDOTRACHEAL INTUBATION

by

Corey Mammen

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Abstract

This manuscript investigates the negative sequelae (in particular, myalgia) of using succinylcholine for patients undergoing tracheal intubation, pretreatment strategies to minimize or eliminate these untoward effects, and compare their efficacy. Various strategies are commonplace in the clinical setting, and there are a number of research studies that discuss the efficacy of individual agents as well as compare them against others. This manuscript explains the anatomy and physiology of neuromuscular junctions, muscle contraction, and their relationship with muscle relaxants used in the clinical setting.

Keywords: succinylcholine, fasciculations, myalgia, pretreatment, depolarizing muscle relaxant, nondepolarizing muscle relaxant

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Comparing Pretreatment Modalities for the Prevention of Succinylcholine-Induced Fasciculations in Adults Undergoing Endotracheal Intubation

Background/Statement of the Problem

Tracheal intubation is a medical procedure that involves inserting a flexible tube into a patient's trachea. This serves to secure the airway for surgical procedures and to facilitate anesthesia drug administration. Tracheal intubation is accomplished by a multi-modal approach that includes sedation, analgesia, and muscle relaxation, which produces paralysis. Paralysis is necessary for this procedure due to the reflex mechanisms of the laryngeal muscles, which surround the trachea (Nagelhout, 2014). Two types of muscle relaxants are used for intubation: depolarizing and non-depolarizing. Succinylcholine is a depolarizing muscle relaxant that is widely used in anesthesia for this purpose because it has many qualities that are recognized as ideal, such as rapid onset, short duration of action, a comfortable margin between muscular relaxation and respiratory depression/arrest, and a controllable intensity. These qualities result in a patient who needs less sedation and paralysis compared to longer-lasting sedatives and paralytic agents. In many cases, intubation needs to occur very rapidly. The advantage of succinylcholine, noted as far back as the 1950s, is its ability to meet these characteristics (Foldes, McNall, & Borrego-Hinojosa, 1952). Succinylcholine's ability to relax muscle fibers in less than a minute, as well as fast recovery time in three to five minutes becomes potentially life-saving in the event of a difficult or failed intubation (Abbas et al., 2009).

The mechanism of action of depolarizing muscle relaxants, such as succinylcholine, is to mimic the neurotransmitter acetylcholine at the postsynaptic

nicotinic receptor. When two alpha subunits of this receptor are occupied, sodium passes through the membrane and depolarizes the cell. When this happens, an action potential occurs, which produces muscle contractions. Generating muscle contractions in order to produce paralysis may seem counter-intuitive; however, succinylcholine produces a sustained depolarization of this receptor, which prohibits it from repolarizing. The inability to repolarize then prevents another depolarization of the cell by inactivating sodium channels, which prevents further muscle contractions (i.e. paralysis). Sustained muscular contractions are known as fasciculations, which may be viewed as visible, fast contractions of muscle fibers. It is through this mechanism that succinylcholine produces several adverse effects, including postoperative myalgia (which can last several days) and increased serum potassium (Hochhalter, 1996). Therefore, minimizing these adverse effects is a concern.

Some drugs, including non-depolarizing muscle relaxants, have been shown to reduce fasciculations, and as a consequence, reduce adverse effects (True & Carter, 2003). Non-depolarizers antagonize the receptor, eliminating the incidence of action potentials. This essentially decreases the number of receptors that succinylcholine can influence, thus reducing fasciculations. A variety of other agents (not muscle relaxants) work by different mechanisms, but still reveal a decreased incidence of fasciculations, such as propofol, magnesium sulfate, lidocaine, and alfentanil (Hochhalter, 1996).

Therefore, the purpose of this project is to conduct a systematic review to compare pretreatment modalities for the prevention of succinylcholine-induced fasciculations in adults undergoing endotracheal intubation, as measured postoperative myalgia. Next, a review of the literature will be presented.

Literature Review

Databases used in this literature review were PubMed, Cinahl, Google Scholar, and Web of Science. Keywords searched were "succinylcholine" and "fasciculations" in the title or abstract. Additional keywords included "depolarizing muscle relaxant," "nondepolarizing muscle relaxant," and "myalgia" and were used in combination with succinylcholine and fasciculations in order to eliminate articles that did not use succinylcholine. There were no restrictions on dates as to not exclude historical literature.

Neuromuscular Junction Physiology and Receptor Theory

Skeletal muscle contraction is mediated by the peripheral nervous system. The site where communication between the sensory and motor neurons occurs is called the neuromuscular junction (NMJ). The NMJ is composed of three elements: the presynaptic sensory nerve, the postsynaptic motor membrane, and the synaptic cleft which lies between the two membranes. In order for communication to take place, an action potential must take place. An action potential is the response of a cell to an electrical impulse, which is mediated by the exchange of intracellular and extracellular electrolytes, which is known as depolarization. This occurs when the electrical charge of a cell rises above a certain threshold (Omar & Bollu, 2019). Immediately after depolarization occurs, the cell will begin to repolarize which allows it to receive another signal after a short refractory period. When depolarization occurs on the presynaptic membrane, the neurotransmitter acetylcholine is released from the presynaptic structure of the sensory neuron, crosses the synaptic cleft, and attaches to nicotinic receptors on the postsynaptic structure. Each receptor has five subunits (the specific site of attachment):

two alpha (α), and one each of beta (β), delta (δ), and epsilon (ε) subunits. Acetylcholine only attaches to the alpha subunits. Furthermore, an action potential is possible only when both alpha subunits are occupied by acetylcholine (Dani, 2015). When this happens, the receptor undergoes a structural change, allowing sodium into that cell. This produces an action potential in the cells of the motor neuron and eventually stimulates the sarcoplasmic reticulum of the muscle to release calcium, which causes muscle contraction (Kuo & Ehrlich, 2015).

In the synaptic cleft, the enzyme acetylcholinesterase is available in large quantities to begin breaking down and recycling acetylcholine; this process begins almost immediately. If this does not happen, muscular contraction would be sustained due to the increased availability of acetylcholine. Therefore, acetylcholinesterase is the body's regulatory mechanism, which allows muscles to return to a resting state (Nagelhout, 2014).

Neuromuscular blocking agents

Muscle relaxants are medications administered that purposefully induce relaxation. In anesthesia, the muscles are relaxed to the extent that paralysis occurs, which is necessary for endotracheal intubation as well as many surgical procedures. These medications block skeletal muscle action potentials by various mechanisms. Each drug has a specific profile which includes its mechanism of action, speed of onset, duration of action, and potential side effects. Neuromuscular blocking agents (NMBAs) are divided into two classes: non-depolarizers and depolarizers (Gulenay & Mathai, 2018).

Non-depolarizing agents. The mechanism of action of the non-depolarizing agents is to competitively block the alpha subunits of the postsynaptic receptor. This inhibits acetylcholine from occupying the site of action (Clar & Liu, 2019). This inhibition essentially inactivates the receptor, which prohibits any further action potentials. As a result, muscle contractions are prohibited for the life of that agent, which are determined mostly by metabolism and redistribution. Metabolism depends on the agent: some are metabolized in the liver, while others are metabolized by plasma enzymes. Redistribution involves the movement of a drug in the body's circulation, which supplies various "compartments." These compartments include those with high blood flow and those with low blood flow. The heart, lungs, brain, kidneys, and liver are considered high blood flow areas, while muscle, bone, and adipose tissue are examples of low blood flow structures. A drug is essentially terminated when it is redistributed to tissue compartments that have lower blood flow levels (such as adipose tissue) since there are no receptors for the drug in that tissue (Nagelhout, 2014).

Depolarizing agents. The mechanism of action of depolarizing agents may at first seem counterintuitive, since they produce depolarization and an action potential of the postsynaptic motor neuron, producing muscle contraction. The only depolarizing agent used in the United States (U.S.) is succinylcholine (Gulenay & Mathai, 2018). The molecular structure of succinylcholine is identical to two molecules of acetylcholine. Therefore, succinylcholine easily binds to both alpha subunits on the postsynaptic receptor and produces an action potential, generating muscle contraction. However, because succinylcholine is not susceptible to the same enzyme that breaks down acetylcholine, it remains attached to the receptor. This attachment produces a sustained

flow of sodium into the cell and therefore a series of muscle contractions, known as fasciculations. By maintaining the electrical charge above the threshold, because of the continued influx of sodium, it prohibits the cell from repolarizing. After a few moments, this sustained depolarization eventually causes the receptors to become desensitized. The muscle finally relaxes but because the receptors are still occupied by succinylcholine, further depolarization is not possible until the succinylcholine disassociates and is metabolized by different enzymes (Nagelhout, 2014).

Muscle Contraction Physiology

A cascade of events takes place when a signal is sent from the brain to a muscle group by motor neurons, called a motor unit. On the presynaptic side of the NMJ, the action potential opens calcium channels, and there is an influx of calcium, a positively charged electrolyte, into the neuron. This increased positive charge causes vesicles that contain acetylcholine to migrate to the outer membrane and begin the process that ends with its rupture, which releases acetylcholine into the synaptic cleft. Some acetylcholine crosses the cleft and attaches to the two alpha subunits of the nicotinic receptor while others are almost immediately bound to acetylcholinesterase to begin the regulatory process. On the postsynaptic side, another action potential is triggered when enough acetylcholine attaches to their respective receptors, allowing an influx of sodium into that cell. Thousands or millions of cells are clustered together in the matrix outside of the sarcoplasmic reticulum (SR). Action potentials (electrical impulses) are essentially generated simultaneously, which causes cells in the SR to release calcium. It is this release of calcium that causes a unified contraction of muscle fibers (Kuo & Ehrlich, 2015).

The importance of the contraction of skeletal muscles to animal life is obvious: without skeletal muscle contractions, one could not walk, talk, eat, or breathe. Several physiologic changes occur with the continued use of muscle groups. Anyone who has been involved in physical exercise (from walking to weight training) knows some of these intuitively: body temperature rises, and one may end up with sore muscles the following day. These are normal and essentially expected results of using muscles in a strenuous fashion; however, many changes take place at the cellular level, which in turn have the potential to produce a cascade of events that move beyond those rudimentary actions necessary to life (Nagelhout, 2014).

Potential Adverse Effects of Sustained Muscle Contraction

When a cell depolarizes, one of the electrolyte exchanges that occurs is between sodium and potassium. As mentioned previously, sodium (the primary extracellular positively charged ion) enters the cell when it is depolarized. At the same time, potassium, the primary intracellular positively charged electrolyte, leaves the cell. During sustained depolarization, since potassium is unable to reenter the cell, it is introduced into the plasma. Potassium is regulated within tight margins in serum plasma by the kidneys (3.5 – 5.0 mmol/L); too little or too much can have devastating effects on cardiac function, including death (Nagelhout, 2014). The sustained contractions by succinylcholine can increase plasma potassium up to 0.5 mmol/L (Hager, 2019). Nagelhout (2014) suggests possible increases of up to 1.0 mmol/L. High plasma potassium levels over 5.5 mmol/L is considered hyperkalemia, while levels higher than 6.0 mmol/L can produce serious cardiac events and may require immediate treatment. A modest increase is usually insignificant in terms of clinical practice; however, if a patient

has high potassium levels at baseline (e.g. due to kidney disease), this becomes especially dangerous. Other patient populations that are susceptible to adverse effects of hyperkalemia are burn and trauma victims and therefore succinylcholine is contraindicated in these patients (Hager, 2019).

Continued muscular contraction increases the tissue's oxygen requirements, which in turn increases the body's basal metabolic rate. This increased metabolism is the mechanism by which energy is changed into the form of heat. The sustained contraction of muscles uses more oxygen than is supplied. Muscle tissue then changes from aerobic to anaerobic metabolism, which produces lactic acid, which is converted to lactate and hydrogen ions. It is the lactate that builds up in the muscle tissue that causes pain in subsequent days. Elevated temperature (hyperthermia) and muscle pain (myalgia) are also potential adverse effects of succinylcholine-induced fasciculations (Gulenay & Mathai, 2018).

Pain. Pain is an incredibly complex concept that involves various categories and descriptions. For example, it may be classified in terms of longevity (chronic vs. acute) and/or the underlying source (nociceptive vs. non-nociceptive). Nociceptive pain involves the stimulation of specific nerve endings in specific locations of the body that produce a pain response. Alternately, non-nociceptive pain involves damage to structures of the central or peripheral nervous systems. This type of pain often has no identifiable cause. Additionally, it is multidimensional in the way it is experienced, involving sensory and emotional components (Nagelhout, 2014).

Several neurotransmitters (NT) and chemicals in the body serve to enhance or suppress pain signals. These include Substance P, bradykinin, prostaglandins, serotonin,

and glutamate among several others. As some form of tissue damage occurs, these chemicals and NT stimulate nociceptors and a pain impulse is generated. This impulse is then transmitted from the peripheral nervous system (PNS) to the central nervous system (CNS), which includes the spinal cord and brain. By a complex communication system, these pain signals ascend the spinal cord and are finally perceived as pain in various locations in the brain. The brain then sends signals back through the spinal cord to be transmitted to the periphery. At that point, motor, chemical, and/or physiologic responses occur. For example, a motor response includes the removal of a hand from a painful stimulus (like a hot stove). A chemical response includes the release of chemicals that influences further pain perceptions. Finally, physiologic responses include a faster heart rate, faster respiration rate, swelling at the site of injury, and other reactions (Nagelhout, 2014).

Pain, including postoperative pain and myalgia (muscle pain) affects various populations differently. Regarding postoperative pain, there is a lower incidence in males, those who take part in muscular exercise or activity, and patients at both extremes of age (the very old and the very young). Pain also occurs with increased severity in patients who ambulate earlier in the postoperative period. Additionally, there is a constellation of factors that may either mask or exaggerate pain in general, such as biologic, cultural, emotional, and social considerations (Nagelhout, 2014).

The issue of pain becomes clinically significant because of the relationship between patient perceptions of pain, associated stress, and delayed healing time. Healing is a complex continuum with several stages including inflammation, tissue remodeling, and hemostasis. At the proper time, in the proper sequence, and for the proper duration

of time, these stages must occur for healing to occur. Pain is one of many factors that can influence wound healing by interfering with this process (Guo & DiPietro, 2010). Therefore, the reduction of stimuli that causes pain, including myalgias, should be a significant focus in the clinical setting.

Myalgia. The sustained contraction of muscle fibers during succinylcholine administration often produces postoperative myalgia, which may be delayed up to the fourth postoperative day. However, the presence or absence of fasciculations is not predictive of subsequent myalgia. Some patients may experience fasciculations but have no postoperative myalgia, while others may have no visible fasciculations yet suffer from postoperative myalgia (Abbas et al., 2009). Similar to general pain, myalgia tends to affect populations differently. Some factors include patient age, surgical position, and type of surgery. Additionally, males tend to have fewer complaints of myalgia than females (Hochhalter, 1996). It is unknown if these factors may or may not have any connection to the use of succinylcholine. Therefore, one cannot definitively conclude that postoperative myalgia is a consequence of succinylcholine administration as opposed to one or more of these other factors.

Myalgia occurs due to the activation of nociceptors, which are receptors that are specialized to respond to tissue-damaging stimuli. The tissue damage is then perceived subjectively as pain. Stimuli are generally either mechanical or chemical in origin. Tissue trauma is an example of mechanical stimuli, while adenosine triphosphate (ATP), protons (H+ ion), and substance P (SP) are examples of chemical stimuli. Additionally, pathophysiological alterations of tissue are accompanied by a decrease in potential hydrogen (pH), making the tissue acidic. An acidic pH level in muscle tissue is a major

factor that leads to muscular pain (Mense, 2008). In this context, chemical activation is the factor to be considered. Specifically, muscular exercise in the absence of oxygen produces lactate as a byproduct. Lactate has been implicated as a contributing factor in pain because it acts on muscular innervation of sensory neurons (Ishii & Nishida, 2014).

Free radicals. An additional byproduct of muscle contractions (and subsequent metabolism and cellular function) are free radicals (FR), which can be both beneficial and toxic to the body. The body produces endogenous antioxidants, but at times the production of FR exceeds the capabilities of the body's natural FR "scavengers." When FR accumulate in the body, a process called oxidative damage occurs. This refers to damage done to a wide array of biomolecules in an indiscriminate and arbitrary manner, which then contributes to pain. Simioni et al. (2017) demonstrated that a relationship exists between pain and oxidative stress. Murphy, Myers, Davies, Webster, and Jones (1992) note that FR in some way contribute to tissue injury, resulting in many acute conditions. Free radicals have been suggested as causing postoperative myalgia. Recently, antioxidants have been investigated as having a potential pain-relieving mechanism. Propofol is one such FR scavenger, and both single-dose and continuous intravenous infusions have been effective in preventing postoperative myalgia connected with succinylcholine administration (Kararmaz, Kaya, Turhanoglu, & Ozyilmaz, 2003). Since pain is a complex concept with varying pathways in the body, it makes sense that a diversity of agents (not simply non-depolarizing muscle relaxants), are being used in the prevention of myalgias associated with succinylcholine.

Measuring Fasciculations and Pain

Measuring Fasciculations. Visible signs and symptoms of many disease processes can be subjective, and muscle fasciculations are no different. In a study done by Abbas et al. (2009), fasciculations were measured using a four-point scale from a prior study from 1987. The authors used a four-point numeric tool that scored fasciculations from 00 (no fasciculations) to 03 (severe fasciculations). Mild fasciculations were scored as 01, while 02 indicated moderate fasciculations. However, even though the difference between the absence and presence of fasciculations is essentially binary, the difference between large muscle twitches and major limb movements may be subjective depending on the clinician. One may interpret major muscle movement as limb movement, in part because limbs often contain major muscle groups. Additionally, if a patient were in a supine position, an anesthesia provider could not visibly observe fasciculations of back muscles. A study by Khan, Siddiqi, Anjum, and Hamza (2017) used a similar four-tiered 0-3 scale. Virtually every study that measures fasciculations uses a four-tiered system as described above; the major differences are the specific descriptions of the tiers.

Measuring Pain. At baseline, pain scores are subjective in nature. Pain perception varies in patients with functional abilities or disabilities. Other factors such as personal motivation, social supports, cultural, and psychological factors also have an effect on pain perception. The continuum of healthcare has brought us to the current use of a 0-10 pain scale. While this can be very helpful, it has drawbacks due to the subjective nature of pain and varying levels of sensitivity and tolerance (Krebs, Carey, & Weinberger, 2007). Abbas et al. (2009) cite a 1962 study which measures pain as it relates to functional disability. This measurement tool was also a four-point numeric

scale ranging from 00 to 03; 00 indicated no pain, while 03 indicated pain that involved more than one site and included functional disability. Khan et al. (2017) also used a 0 –3 pain scale. The authors not only described levels 1 –3 as mild, moderate, and severe, they also included the relative necessity of treatment (e.g. level 1 required no treatment, level 2 required treatment, and level 3 required additional treatment).

Pretreatment Modalities

Over the decades, clinicians have been experimenting with a variety of ways to attenuate succinylcholine-induced fasciculations. This includes drugs from several drug classes, which work by various mechanisms of action, and include opioids, anti-epileptics, non-steroidal anti-inflammatory agents, gamma aminobutyric acid (GABA) agonists, and others (Khan et al., 2017).

Non-depolarizing muscle relaxants. Because of the mechanism of action of this drug class described above, there are fewer receptors available for succinylcholine to occupy. This produces action potentials that are not as intense or sustained as they would otherwise be if succinylcholine had full access to all receptors. For this reason, this drug class has been highly popular as regards a pretreatment strategy. It has also been frequently studied and shown to be efficacious for this purpose.

GABA agonists. Propofol, gabapentin, and pregabalin are drugs that act on the receptor that deals with the neurotransmitter GABA, which is the body's main inhibitory neurotransmitter. As an inhibitory neurotransmitter, it blocks particular brain signals, which tends to decrease activity in the nervous system. Since fasciculations are a function of the nervous system, inhibiting these signals has been found to block fasciculations to some degree. Gabapentin and pregabalin in particular potentiate GABA

as well as inhibit the release of calcium ions inside neurons and muscle cells (Khan et al., 2017).

Magnesium sulphate. Magnesium sulphate's exact functions are controversial, but it has been shown to minimize two undesirable facets of intubation. First, as an adrenergic antagonist, it blocks catecholamine release during laryngoscopy, including raised heart rate and blood pressure. Second, it has been shown to decrease fasciculations. The authors of one study state that it controls the increase of potassium concentration, thereby attenuating muscular action potentials (Ahsan et al., 2016). However, Sakuraba et al. (2006) state that while it does decrease fasciculations, it has no effect on potassium concentration. Therefore, while it has efficacy in reducing fasciculations, its exact mechanism remains under debate.

Opioids. Opioids, especially remifentanil, have been used in both the induction and maintenance phases of anesthesia for decades. Like magnesium sulphate, they blunt the sympathetic response to laryngoscopy. They also have been shown to reduce the intensity of succinylcholine-induced fasciculations, although the mechanism by which this occurs remains unexplained (Yun et al., 2010).

Next, the theoretical framework will be discussed.

Theoretical Framework

Random controlled trials (RTCs) are individual snapshots of the overall portrait of a particular topic. Each trial, regardless of sample size, contributes information to the larger body of literature. Dozens or hundreds of trials are conducted in various institutions, cities, and countries around the world. An analysis of related studies that compare results is able to greatly enhance the generalizability of the findings, thus making an application in the clinical setting more likely. The collection and distillation of random controlled trials is a necessary step in the research process. Systematic reviews and meta-analyses are tools that enable researchers to synthesize data and attempt to interpret findings in a way that furthers the scope and enhances the knowledge base of a particular area of research. Additionally, systematic reviews may assist in assessing the quality of studies in terms of methods and processes (Liberati et al., 2009).

Systematic reviews are facilitated by frameworks such as the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA). Using this framework enables one to compile and examine the strengths and weaknesses of each RCT, thus revealing a wide-angle viewpoint instead of a close-up, focused glimpse of a topic. PRISMA is an accepted protocol for systematic reviews largely because the flow and results depend heavily on both the scope and quality of the studies included. Therefore, the PRISMA Statement (Figure 1) was developed to guide the authors of systematic reviews. The Statement is a checklist consisting of twenty-seven items as well as a flowchart (Figure 2) to follow step by step. In using these, PRISMA helps to govern the analysis of RCTs, thus maintaining consistency among systematic reviews and meta-analyses (Liberati et al., 2009).

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	19-22

Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	23
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	23
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	23-24
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	24
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	24-25
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	24
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	37
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n/a
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	24

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	37
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	27
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	24
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	28-34
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	37
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	33-34
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	34
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	37
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	34

DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	34-36
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	36-37
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	38
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	n/a

Figure 1. Completed PRISMA checklist

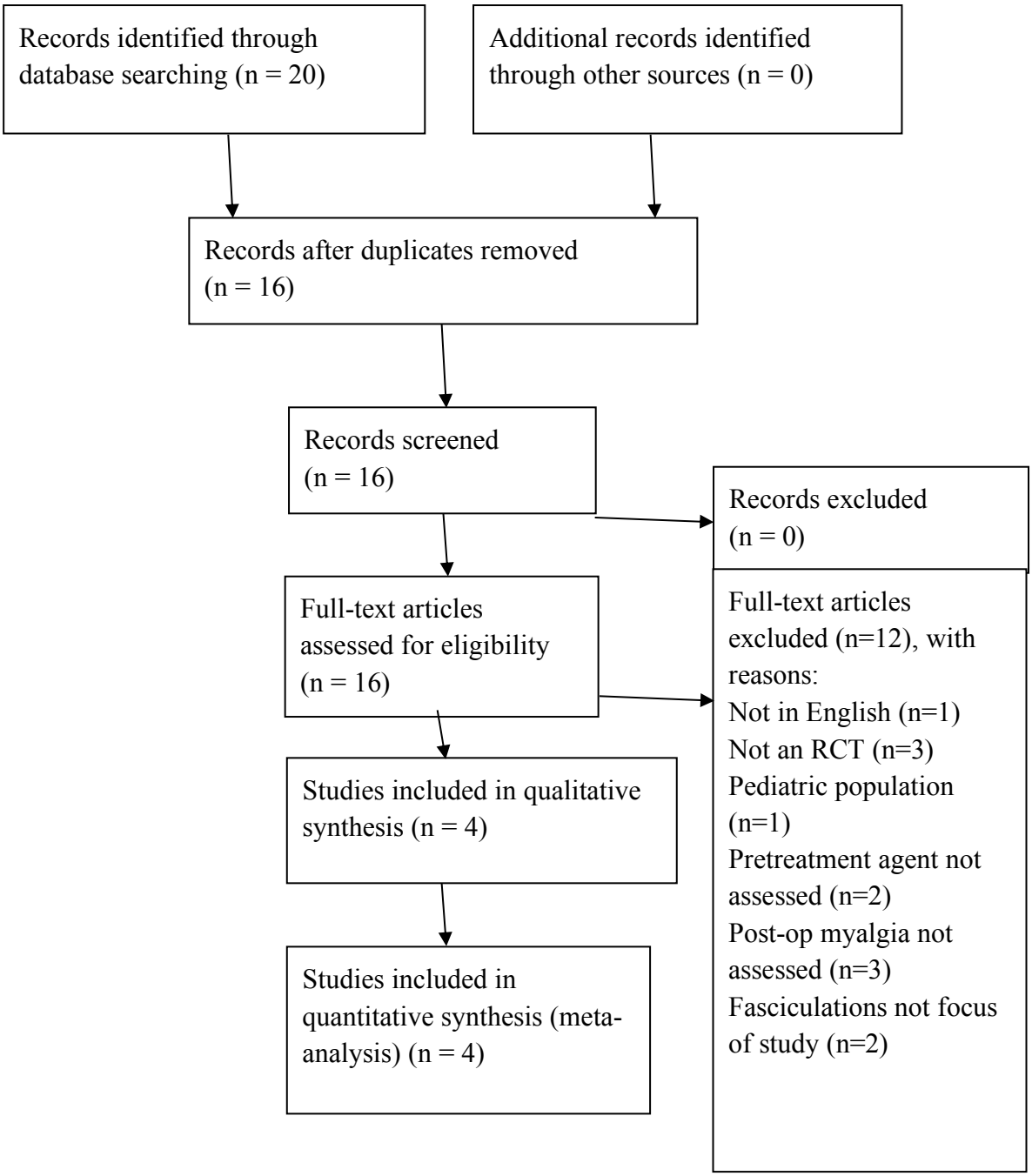

Figure 2. Completed PRISMA flowchart

Next the methods will be discussed.

Methods

Purpose

The purpose of this project was to conduct a systematic review to compare pretreatment modalities for the prevention of succinylcholine-induced fasciculations in adults undergoing endotracheal intubation. The research question that will be examined is: Of the known and available pretreatment modalities for the prevention of succinylcholine-induced fasciculations, which modality has the greatest efficacy as measured by postoperative myalgia?

Inclusion and exclusion criteria

Inclusion criteria were: (1) randomized controlled trials from 2010 to 2020, (2) in adult patients aged 18 and older, (3) with a primary focus on succinylcholine-induced fasciculations, (4) American Society of Anesthesiologists (ASA) classes I and II, (5) and written in English. Pediatric studies were excluded due to significant physiological differences in organ maturation, drug metabolism, medication dosing, and drug response (Nagelhout, 2014). The ASA classifies patients according to physical status with regards to the presence & severity of systemic disease (e.g. hypertension, diabetes, heart failure), using class I through V. Class III and above indicate patients with severe systemic disturbances that either limit activity or are life-threatening, or those for whom surgery is a resuscitative effort, with a minimal chance of survival (Nagelhout, 2014). Therefore, class III and above were excluded due to these confounding factors.

Search strategy

PubMed and Web of Science were searched for randomized controlled trials using the following search criteria: (1) randomized clinical trials, (2) “succinylcholine” in title

or abstract, (3) “fasciculation*” in title or abstract, and (4) date range 2010 to 2020. Fasciculation was searched using the wildcard “*” to capture both “fasciculation” and “fasciculations.” The PubMed search initially yielded eleven studies (n=11) and the Web of Science search yielded nine (n=9), for a total of twenty studies. Four were rejected as duplicates, two were rejected because the study was not examining a pretreatment agent, two were rejected because fasciculations were not the focus of the study, one was rejected because English was not the primary language, one was rejected because pediatric patients were included, three were rejected because the studies did not assess postoperative myalgia, and three were rejected because the studies were not randomized controlled trials. This yielded a total of four studies that were included in this systematic review.

Data collection and synthesis approach

The results of each RCT were placed in two tables. Table 1 displays data that was collected from each RCT and includes the author, sample size, dose of succinylcholine, pretreatment agent, and the percentage of patients with fasciculations at each level of a 4-point scale. Table 2 will display data that reflects the author, pretreatment agent utilized, the time-frame myalgia was measured in (hours postoperative), as well as incidence and severity of myalgia (using a similar 4-point scale).

Sample Table 1

Author	Sample size (n)	Dose Succinylcholine (mg/kg)	Pretreatment agent	Patients with fasciculations (intervention group)	Patients with fasciculations (control group)
				0 = 1 = 2 = 3 =	0 = 1 = 2 = 3 =

Sample Table 2

Author	Dose Succinylcholine (mg/kg)	Pretreatment agent	Myalgia at 24 hrs postoperative (intervention group)	Myalgia at 24 hrs postoperative (control group)
			0 = 1 = 2 = 3 =	0 = 1 = 2 = 3 =

Critical appraisal instruments

The Critical Appraisal Skills Programme (CASP) will be used to critically appraise each RCT (Figure 3). The Critical Appraisal Skills Programme contains eleven questions that are applied to each study. The answers to these questions are analyzed to determine the validity, relevance, trustworthiness, and usefulness of studies. Within the first two questions, it can be determined if that particular study is valid enough to continue the appraisal (Critical Appraisal Skills Programme [CASP], 2017). By critically appraising each RCT, conclusions and results are anticipated to be sufficient to make informed conclusions and recommend further research in this area.

A. Are the results of the trial valid?	**YES**	**CAN'T TELL**	**NO**
1. Did the trial address a clearly focused issue?			
2. Was the assignment of patients to treatments randomized?			
3. Were all of the patients who entered the trial properly accounted for at its conclusion?			
4. Were patients, health workers, and study personnel "blind" to treatment?			
5. Were the groups similar at the start of the trial?			
6. Aside from the experimental intervention, were the groups treated equally?			
B. What are the results?			
7. How large was the treatment effect?			
8. How precise was the estimate of the treatment effect?			
C. Will the results help locally?	**YES**	**CAN'T TELL**	**NO**
9. Can the results be applied in your context?			
10. Were all clinically important outcomes considered?			
11. Are the benefits worth the harms and costs?			

Figure 3. Critical Appraisal Skills Programme (CASP) randomized control trials checklist

Cross Analysis

After critically appraising each randomized control trial utilizing CASP, the studies will be evaluated to compare similarities and differences across the studies. Fasciculations and postoperative myalgia will be assessed according to a 24-hour timeframe, which all studies reviewed used. These will be divided into two columns: none to mild with a score of 0 or 1, or moderate to severe with a score of 2 or 3 (table 3).

Sample Table 3 – Cross Analysis Tool

Author	Pretreatment Agent	Fasciculation score of 0 or 1	Fasciculation score of 2 or 3	Myalgia score of 0-1 at 24 hrs	Myalgia score of 2-3 at 24 hrs

Dissemination of Findings

Ideally, findings of a systematic review should influence clinical practice if the findings are significant. With this in view, the optimal audience would be anesthesia providers. At present, a major paper and poster presentation will be used for initial dissemination.

Next, the results of this systematic review will be presented.

Results

The completed PRISMA flow diagram in the theoretical framework section (Figure 2) demonstrates the process used which yielded the final four studies that were reviewed, as described in the search strategy of the methods section. The results from each of these studies were placed in Tables 1 and 2. Cross analysis was performed and the results were placed in Table 3. All of these appear at the end of the results section. Additionally, a CASP table was completed for each study (Appendix A).

Yun et al. (2010) evaluated the use of remifentanil as a pretreatment modality. In this double-blind study, two equal groups (n=20) of adult patients were analyzed under controlled intubating conditions. One group received remifentanil while the other received normal saline. Both subjective and objective means were utilized to determine presence and severity of fasciculations. The intensity and duration of fasciculations were noted and recorded following administration of succinylcholine. 90% of the control group experienced fasciculations while 85% of the intervention group experienced fasciculations. Further, the duration of fasciculations in the intervention group was 41.6 seconds vs. 59.6 seconds in the control group. Myalgia was recorded twenty-four hours after the time of induction. Objective data included the use of electromyography whereby muscle action potentials are measured using electrodes. Recordings of the amplitude of the action potentials are able to quantify the degree of fasciculations. Additionally, serum potassium levels were analyzed five minutes after succinylcholine administration and creatine kinase (CK) levels were analyzed twenty-four hours after induction time. Both potassium and CK give an indication of muscle activity and cellular breakdown. The results showed a decrease in the intensity of fasciculations in the

remifentanil group, but similarities were found in both incidence and duration of fasciculations between the groups. With respect to myalgia, there was no statistically significant difference between the two groups: only one patient experienced mild myalgia in the remifentanil group, and only two experienced mild myalgia in the control group. Moderate and severe myalgia were absent in both groups. The authors concluded that remifentanil was able to attenuate the intensity of fasciculations but produced no notable effect on postoperative myalgia. The authors suggested that dosing regimens could be studied and potentially optimized for this use.

Khan, Siddiqi, Anjum, & Hamza (2017) performed a randomized controlled study using pregabalin, an anti-epileptic drug that acts on the neurotransmitter GABA. Seventy patients were divided into two equal groups. The control group received a placebo pill while the intervention group were administered 150 mg of pregabalin, both two hours before induction of anesthesia and administration of succinylcholine. Fasciculation incidence and intensity was measured using a four-point scale by a blinded resident doctor. Additionally, 24 hours after the surgery, myalgia was assessed using a similar four-point scale. The results demonstrated a significant difference between the incidence and severity of myalgia in the first 24 hours of the postoperative period ($p=0.000$). However, the incidence of fasciculations was not statistically significant between the two groups ($p=0.096$), although the severity seemed to be decreased in the intervention group. Further, all patients who received pregabalin tolerated it well, and none experienced any significant side effects of the drug (e.g. somnolence). Limitations of this study include the fact that it was a single type of surgical procedure (laparoscopic cholecystectomy) at a single site. However, a wider scope of surgical procedures will most likely not influence

generalizability to any significant degree since the only issue being assessed is fasciculations associated with the induction/intubation period. Since postoperative myalgia is being assessed, one issue may be that other procedures have a higher degree of postoperative pain associated with them. This may influence a patient's assessment of myalgia that is strictly due to fasciculations.

Pandey, Tripathi, Joshi, Karna, Singh, and Singh (2012) studied gabapentin, another anti-epileptic drug similar to pregabalin. Seventy patients participated in this study. The intervention group (n=35) received an oral dose (600 mg) of gabapentin two hours prior to surgery while the control group (n=35) received a placebo (also administered orally). 1.5 mg/kg of succinylcholine was used in both groups, and all other adjunct medications (fentanyl, thiopentone, and maintenance drugs) were the same. The results showed a significant decrease in the postoperative incidence and severity of myalgia ($p<0.05$) between the groups. In the control group, twenty experienced myalgia in the first 24 hours postoperative. This was contrasted with only eleven in the intervention group experiencing myalgia in the same time period. There was no statistically significant difference on the incidence or severity of fasciculations between the groups. However, since myalgia involves the patient's perception of pain and/or discomfort, it is a more significant measure of the efficacy of a pretreatment drug as compared to the measure of the incidence and/or severity of fasciculations, which the patient is unaware of. An additional discovery in this study was that the use of gabapentin decreased the need for intra-operative pain medications, measured by the administration of fentanyl. As with Khan et al., this study assessed only laparoscopic cholecystectomy procedures at a single site.

Vyankatesh, Kiran, and Satish (2016) performed a study that compared two non-depolarizing muscle relaxant drugs against both one another as well as a control group. One hundred fifty patients were divided into three equal groups of fifty. Group NS (control group) received 2 mL of normal saline, group V received 0.1 mg/kg of vecuronium, and group R received 0.06 mg/kg of rocuronium for pretreatment. ASA I & II patients of both genders with a mean age between 35.5 and 37.3 were included in this study. The results showed that the group that received rocuronium had the largest number of patients with fasciculations graded as 0 or 1 (100%), followed by the group that received vecuronium (88%). The control group had just 28% with a 0 or 1 grade. The inverse was true regarding fasciculations with a grade of 2 or 3: the control group (group NS) had 72% at that severity level, group V had 24%, while group R had 0%. Concerning postoperative myalgia at 24 hours out, the results essentially followed those regarding fasciculations, as displayed in table 3. Group R had the highest percentage in the 0 category, followed by group V and then by group NS. As for scores 1, 2, and 3 (mild, moderate, and severe, respectively) on the four-point myalgia scale, group NS had the most of all three groups at each level, followed by group V, with group R showing the least percentage of postoperative myalgia of all groups. Of note, this was the only study in this review that assessed myalgia at a postoperative timeframe of greater than 24 hours. The results basically mirrored those of postoperative day 1. However (and interestingly), the percentages of all three groups at level 0 (no myalgia) decreased, while those of the other levels of myalgia increased with only a few exceptions: at no assessment was there level 3 myalgia in group V, and at no assessment were there levels 2 or 3 in group R.

One error was noted in the fasciculation-scoring table of this study for the group that received vecuronium: the amount of participants added up to 56 instead of 50; therefore, the percentages also ended up high (112%). This was the only table noted to have this error; all others correctly added up to a total of 50 in the group. These incorrect results are still included in this systematic review as they appear in the study; however, the reader should be aware that the results are not completely accurate as regards fasciculations. Since the myalgia scores are the main end focus of this review, the study in its entirety was not excluded since the data from the myalgia table added up correctly.

This study when compared to the other three displayed more tables showing a greater breadth of clinically relevant outcomes. These included urine myoglobin, serum CPK levels, and serum potassium levels, all of which are relevant sequelae of succinylcholine administration.

Table 1 – Data Collection Tool 1 – RESULTS

Author	Sample size (n)	Dose Succinylcholine (mg/kg)	Pretreatment agent	Patients with fasciculations (intervention group)	Patients with fasciculations (control group)
Yun et al., 2010	n=40	1	Remifentanil	0 = 15% 1 = 65% 2 = 20% 3 = 0%	0 = 10% 1 = 5% 2 = 60% 3 = 25%
Khan et al., 2017	n=70	1.5	Pregabalin	0 = 8.5% 1 = 48.5% 2 = 40 % 3 = 3%	0 = 8.5% 1 = 28.5% 2 = 43% 3 = 20%
Pandey, Tripathi, Joshi, Karna, Singh, & Singh, 2012	n=70	1.5	Gabapentin	0 = 14% 1 = 46% 2 = 34% 3 = 6%	0 = 17% 1 = 23% 2 = 49% 3 = 11%

Vyankatesh, Kiran, & Satish, 2016	n=150	1.5	Rocuronium (vs.) Vecuronium* * results add up to 112% as noted	0 = 76% 1 = 24% 2 = 0% 3 = 0% 0 = 52% 1 = 36% 2 = 12% 3 = 12%	0 = 0% 1 = 28% 2 = 60% 3 = 12%

Table 2 – Data Collection Tool 2 – RESULTS

Author	Pretreatment agent	Myalgia at 24 hrs postoperative (intervention group)	Myalgia at 24 hrs postoperative (control group)
Yun et al., 2010	Remifentanil	0 = 95% 1 = 5% 2 = 0% 3 = 0%	0 = 90% 1= 10% 2 = 0% 3 = 0%
Khan et al., 2017	Pregabalin	0 = 31.4% 1 = 54.3% 2 = 14.3% 3 = 0%	0 = 6% 1= 29% 2 = 51% 3 = 14%
Pandey et al., 2012	Gabapentin	0 = 57% 1 = 31.5% 2 = 11.5% 3 = 0%	0 = 31% 1= 40% 2 = 29% 3 = 0%
Vyankatesh, Kiran, & Satish, 2016	Rocuronium Vecuronium	0 = 88% 1 = 12% 2 = 0% 3 = 0% 0 = 72% 1 = 20% 2 = 8% 3 = 0%	0 = 16% 1= 52% 2 = 24% 3 = 8%

Table 3 – Cross Analysis Tool - RESULTS

Author	Pretreatment Agent (pretreatment modality)	Fasciculation score of 0 or 1	Fasciculation score of 2 or 3	Myalgia score of 0-1 at 24 hrs	Myalgia score of 2-3 at 24 hrs
Yun et al., 2010	Remifentanil	80%	20%	100%	0%
Khan et al., 2017	Pregabalin	57%	43%	85.7%	7.1%
Pandey et al., 2012	Gabapentin	60%	40%	88.5%	11.5%
Vyankatesh, Kiran, & Satish, 2016	Rocuronium vs. Vecuronium* * fasciculation results add up to 112% as noted	100% 88%	0% 24%	100% 92%	0% 8%

Summary and Conclusions

Succinylcholine is a popular muscle relaxant useful in a number of tracheal intubation situations, particularly rapid sequence intubation (RSI). Its rapid onset and metabolism by innate enzymes make it an ideal choice for this purpose, especially when coupled with shorter procedures which do not require longer lengths of time of muscle relaxation. However, its side effect profile includes fasciculations, which quite often produce myalgias in the immediate postoperative period (Yun et al., 2010). Because of this, clinicians have experimented with a variety of other agents to use as a pretreatment adjunct to succinylcholine in an attempt to attenuate or eliminate fasciculations and myalgias. Many of these other agents, because of their mechanisms of action, have been shown to be beneficial for this purpose, with varying degrees of success.

The purpose of this systematic review was to identify agents that reduce or eliminate fasciculations as evidenced by an absence of postoperative myalgias, compare them using a variety of tools, and attempt to identify a single agent that is superior to the others. The literature review focused on cell receptor theory, the mechanism of muscle contraction, the mechanism of action of muscle relaxant drugs used in anesthesia, and pain. The theoretical framework utilized both PRISMA and CASP, which are considered the gold standard for systematic reviews. The former includes a checklist and flowchart with which to organize, include, or exclude studies depending on their applicability, while with the latter one is able to judge the integrity, validity, and rigor of a study or experiment. Using these in tandem, one may form certain conclusions and identify correlations that may be useful in answering the research question. This analysis was

performed on the four studies that met criteria for inclusion. Cross analysis was then performed on the data that was collected, which establishes certain findings.

To summarize, the results of the cross analysis (Table 3) demonstrate that every agent used to reduce fasciculations was efficacious, to varying degrees. To be clear, even though both rocuronium and remifentanil had myalgia scores of 100% in the 0 or 1 score levels and 0% in the 2 or 3 score levels, there is a vast difference between the two. The difference between the rocuronium and control groups was significant, even though a p value was not specifically given. In the remifentanil study, this percentage reflected only one patient who experienced myalgia, while there were only two in the control group; therefore, this is not statistically significant. However, it is interesting to note that in the remifentanil study (Yun et al., 2010), a total of only 3 participants reported myalgia of any severity, which is not even 1% of the whole. That is a significantly lower percentage than any of the other studies. Perhaps there is a correlation between the dose of succinylcholine as compared to the other studies; in this study, only 1 mg/kg was used, while the other three studies used 1.5 mg/kg. Possibly a reduced dose of succinylcholine would produce acceptable intubating conditions while at the same time mitigating its own postoperative myalgia. Yun et al. did not note any difficult intubating conditions as a result of the lower dose of succinylcholine. Additionally, this was the only study that noted the duration in seconds of the fasciculations. It would be interesting in future research to compare incidence, severity, *and duration* of fasciculations as those factors relate to postoperative myalgia.

This synthesis and evaluation points to the findings of this systematic review. The research question asked which agent was the most efficacious in eliminating or

reducing succinylcholine-induced fasciculations as measured by postoperative myalgia. To this end, it seems that rocuronium, a nondepolarizing muscle relaxant, has the greatest efficacy in the elimination and/or reduction of both the frequency and severity of both fasciculations and myalgia as compared to a control group. However, as noted above, a secondary finding seems to suggest that a lower dose of succinylcholine (with or without a pretreatment agent,) may be used for intubation, and reduce fasciculations. This dosing adjustment may in turn diminish postoperative myalgia.

There were a number of limitations identified while performing this systematic review. Only the most recent studies were included (2010-present). While this focuses on current modalities and clinical practice, it excludes other agents that perhaps have not been studied recently but that are still in use clinically, or agents that are used elsewhere globally that are more accessible and less expensive than their first-world counterparts. In every study, only patients classified as ASA I or II were included, which could limit generalizability. Additionally, only certain procedures were reflected in these studies. Two of these were laparoscopic cholecystectomy, one (Yun et al., 2010) included only elective otolaryngological surgery specifically because it carries a minimal risk of serum CK increases, and the last did not disclose the type(s) of procedure(s). RSI is used in many emergent, trauma, and difficult airway cases; it is difficult to know if there are confounding factors associated with these types of procedures that do not exist in a relatively controlled environment. Additionally, patients with known conditions such as neuromuscular diseases or morbid obesity, and those at the extremes of age were excluded (Yun et al., 2010). Some of these conditions contraindicate the use of succinylcholine (e.g. certain neuromuscular diseases), but others do not; however,

without studying a wider population, including special populations, results may not be generalizable.

Risk of bias is always present in any study; however it can be minimized by being transparent as regards the methods and reporting of the results. These four studies were blinded, randomized controlled trials, with methods clearly communicated and therefore easily duplicated. Therefore, the risk of bias seems quite negligible. However, the subjectivity as regards the reporting of both fasciculations and postoperative myalgia could contain varying degrees of risk of bias. Since pain contains physical, emotional, and psychological elements, the reporting of postoperative pain may be laden with bias: some patients may feel free to report (with or without exaggeration), while others may be relatively stoic in their approach to pain and reporting it.

Recommendations and Implications for Advanced Nursing Practice

The ultimate goal for research is to impact clinical practice. It is obvious that fasciculations associated with the administration of succinylcholine very often produce myalgia for the patient in the postoperative period; this has been a clinical concern for decades. This impacts the patient's perception of the healthcare system in general, which flows down to individual disciplines within the healthcare system, including anesthesia. Therefore, minimizing or eliminating this unpleasant side effect has been, and should continue to be, a focus for APN anesthesia providers. Various drugs that can be used for this purpose are readily available and should be used if there are no contraindications. This would serve to increase the quality of our practice, and in a broad sense be a way that we advocate for our patients' postoperative comfort.

As noted above with the different dosing of succinylcholine, future research could focus on using smaller doses of succinylcholine in conjunction with a pretreatment agent in order to reduce or eliminate myalgia. Centrally located nerves and muscles (e.g. face, throat) are affected before peripheral nerves and muscles (arms, hands, legs); therefore, could an alternate dosing strategy be developed to produce enough paralysis for intubation, without the need to affect 100% of every peripheral receptor?

Results shown here, as well as future research, can be promulgated on a broader scale. This could include various publications and conference presentations. Ultimately, it is up to each individual provider of anesthesia to be an active and critical consumer of research information in whatever form it takes, and seek to implement new, clinically relevant data into practice. Additionally, policy development for the APN is an important facet of clinical practice. This does not always need to be at a national or state level; we

have the ability to develop protocols and policies at individual institutions regarding more comprehensive patient education before a procedure (i.e. possible symptoms they may experience postoperatively) as well as patient follow-up in the postoperative period. This may go a long way to build trust between patients and health care providers.

References

Abbas, N., Tariq, S., Khan, A.W., Murtaza, G., Naqvi, N., Khanzada, A. (2009). To assess the effects of rocuronium pretreatment on succinylcholine induced fasciculations and postoperative myalgias. *Journal of the Pakistan Medical Associates*. 59(12), 847-50. Retrieved from https://www.jpma.org.pk/PdfDownload/1878

Ahsan, B., Rahimi, E., Moradi, A., Rashadmanesh, N. (2014). The effects of magnesium sulphate on succinylcholine-induced fasciculation during induction of general anaesthesia. *Journal of the Pakistan Medical Associates*, 64(10), 1151-3. Retrieved from https://www.jpma.org.pk/PdfDownload/7007.pdf

Clar, D.T. & Liu, M. (2019). Non-depolarizing Neuromuscular Blockers. *StatPearls* Publishing LLC [internet]. Treasure Island, FL. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK534828/

Dani J. A. (2015). Neuronal Nicotinic Acetylcholine Receptor Structure and Function and Response to Nicotine. *International Review of Neurobiology*, 124, 3–19. doi:10.1016/bs.irn.2015.07.001

Foldes, F.F., McNall, P.G., & Borrego-Hinojosa, J.M. (1952). Succinylcholine: A new approach to muscular relaxation in anesthesiology. *New England Journal of Medicine*, 247:596-600

Gulenay, M., & Mathai, J. (2018). Depolarizing Neuromuscular Blocking Drugs. *StatPearls* Publishing LLC [internet]. Treasure Island, FL. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK532996/

Guo, S., & Dipietro, L. A. (2010). Factors affecting wound healing. *Journal of Dental Research*, 89(3), 219–229. doi:10.1177/0022034509359125

Hager H.H., & Burns B. Succinylcholine Chloride. [Updated 2019 Mar 19]. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499984/

Hochhalter, C.M. (1996). Evaluation of succinylcholine-induced fasciculations and myalgias with or without atracurium pretreatment. *Journal of the American Association of Nurse Anesthetists*, 64(4), 336-40. Retrieved from https://pdfs.semanticscholar.org/9a50/f9fca523f12304c130fc078db6676a4c1888.pdf

Ishii, H., & Nishida, Y. (2013). Effect of lactate accumulation during exercise-induced muscle fatigue on the sensorimotor cortex. *Journal of Physical Therapy Science*, 25(12), 1637–1642. doi:10.1589/jpts.25.1637

Kararmaz, A., Kaya, S., Turhanoglu, S., & Ozyilmaz, M.A., (2003). Effects of high-dose propofol on succinylcholine-induced fasciculations and myalgia. *Acta Anaesthesiologica Scandinavica*. Retrieved from https://onlinelibrary.wiley.com/doi/full/10.1034/j.1399-6576.2003.00052.x

Khan, M.A., Siddiqi, K.J., Anjum, K.M., & Hamza, A. (2017). A randomized controlled study on prevention of succinylcholine induced fasciculation and myalgia by pretreatment with pregabalin in patients undergoing laparoscopic cholecystectomy. *Anaesthesia, Pain & Intensive Care*, 21(4). Retrieved from https://www.apicareonline.com/a-randomized-controlled-study-on-prevention-of-

succinylcholine-induced-fasciculation-and-myalgia-by-pretreatment-with-pregabalin-in-patients-undergoing-laparoscopic-cholecystectomy/

Krebs, E.E., Carey, T.S., & Weinberger, M. (2007). Accuracy of the pain numeric rating scale as a screening test in primary care. *Journal of General Internal Medicine*, 22(10), 1453-1458. doi:10.1007/s11606-007-0321-2

Kuo, I. Y., & Ehrlich, B.E. (2015). Signaling in muscle contraction. *Cold Spring Harbor Perspectives In Biology*, 7(2), a006023. doi:10.1101/cshperspect.a006023

Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P., Clarke, M., Devereaux, P.J., Kleijnen, J., & Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* (Clinical research ed.), 339, b2700. doi:10.1136/bmj.b2700

Mense S. (2008). Muscle pain: mechanisms and clinical significance. *Deutsches Arzteblatt International*, 105(12), 214–219. doi:10.3238/artzebl.2008.0214

Murphy, P.G., Myers, D.S., Davies, M.J., Webster, N.R., & Jones, J.G. (1992). The antioxidant potential of propofol (2,6-diisopropylphenol). *British Journal of Anaesthesia*, 68(6): 613-618.

Nagelhout, J.J., & Plaus, K.L. (2014). Nurse Anesthesia (5th ed.). St. Louis, Mo.: Elsevier/Saunders

Omar, A. & Bollu, P. (2019). Physiology, Neuromuscular Junction. *StatPearls* Publishing LLC [internet]. Treasure Island, FL. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK470413/

Pandey, C.K., Tripathi, M., Joshi, G., Karna, S.T., Singh, N., & Singh, P.K. (2012). Prophylactic use of gabapentin for prevention of succinylcholine-induced fasciculation and myalgia: a randomized, double-blinded, placebo-controlled study. *Journal of Postgraduate Medicine*, 58(1). 19-22. doi: 10.4103/0022-3859.93248.

Sakuraba, S., Serita, R., Kosugn, S., Eriksson, L., Lindahl, S., & Takeda, J. (2006). Pretreatment with magnesium sulphate is associated with less succinylcholine-induced fasciculation and subsequent tracheal intubation-induced hemodynamic changes than precurarization with vecuronium during rapid sequence induction. *Acta Anaesthesiology Belg*. 57(3): 253-7.

Simioni, C., Zauli, G., Martelli, A. M., Vitale, M., Sacchetti, G., Gonelli, A., & Neri, L. M. (2018). Oxidative stress: Role of physical exercise and antioxidant nutraceuticals in adulthood and aging. *Oncotarget*, 9(24), 17181-17198. doi:10.18632/oncotarget.24729

Vyankatesh, J.S., Kiran, T.V., & Satish, D.G. (2016). Comparative study of pretreatment with rocuronium and vecuronium in post succinylcholine fasciculation, intubation condition and myalgia. *Journal of Evolution of Medicine and Dental Sciences*, 5:38), 2319-2324. doi: 10.14260/jemds-2016/539

Yun, M.J., Kim, Y.H., Go, Y.K., Shin, J.E., Ryu, C.G., Kim, W., Paik, N.J., Han, M.K., Do, S.H., & Jung, W.S. (2010). Remifentanil attenuates muscle fasciculations by succinylcholine. *Yonsei Medical Journal*, 51(4). Doi.org/10.3349/ymj.2010.51.4.585

Appendices

Appendix A

Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist

Study 1: Yun, M.J., Kim, Y.H., Go, Y.K., Shin, J.E., Ryu, C.G., Kim, W., Paik, N.J., Han, M.K., Do, S.H., & Jung, W.S. (2010). Remifentanil attenuates muscle fasciculations by succinylcholine. *Yonsei Medical Journal*, 51(4).

A) Are the results of the trial valid?	Yes	Can't tell	No
1. Did the trial address a clearly focused issue?	x		
2. Was the assignment of patients to treatments randomized?	x		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	x		
4. Were patients, health workers, and study personnel "blind" to treatment?	x		
5. Were the groups similar at the start of the trial?	x		
6. Aside from the experimental intervention, were the groups treated equally?	x		
B) What are the results?			
7. How large was the treatment effect?	40 otolaryngological patients.		
8. How precise was the estimate of the treatment effect?	No statistically significant decrease in myalgia.		
C) Will the results help locally?			
9. Can the results be applied in your context? (or to the local population)	x		
10. Were all clinically important outcomes considered?			x
11. Are the benefits worth the harms and costs?	x		

Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist

Study 2: Khan, M.A., Siddiqi, K.J., Anjum, K.M., & Hamza, A. (2017). A randomized controlled study on prevention of succinylcholine induced fasciculation and myalgia by pretreatment with pregabalin in patients undergoing laparoscopic cholecystectomy. *Anaesthesia, Pain & Intensive Care*, 21(4).

A)	**Are the results of the trial valid?**	**Yes**	**Can't tell**	**No**
1.	Did the trial address a clearly focused issue?	x		
2.	Was the assignment of patients to treatments randomized?	x		
3.	Were all of the patients who entered the trial properly accounted for at its conclusion?	x		
4.	Were patients, health workers, and study personnel "blind" to treatment?	x		
5.	Were the groups similar at the start of the trial?	x		
6.	Aside from the experimental intervention, were the groups treated equally?	x		
B)	**What are the results?**			
7.	How large was the treatment effect?	70 laparoscopic cholecystectomy patients.		
8.	How precise was the estimate of the treatment effect?	Decrease of myalgia was statistically significant.		
C)	**Will the results help locally?**			
9.	Can the results be applied in your context? (or to the local population)	x		
10.	Were all clinically important outcomes considered?			x
11.	Are the benefits worth the harms and costs?	x		

Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist

Study 3: Pandey, C.K., Tripathi, M., Joshi, G., Karna, S.T., Singh, N., & Singh, P.K. (2012). Prophylactic use of gabapentin for prevention of succinylcholine-induced fasciculation and myalgia: a randomized, double-blinded, placebo-controlled study. *Journal of Postgraduate Medicine*, 58(1). 19-22.

A)	**Are the results of the trial valid?**	**Yes**	**Can't tell**	**No**
1.	Did the trial address a clearly focused issue?	x		
2.	Was the assignment of patients to treatments randomized?	x		
3.	Were all of the patients who entered the trial properly accounted for at its conclusion?	x		
4.	Were patients, health workers, and study personnel "blind" to treatment?	x		
5.	Were the groups similar at the start of the trial?	x		
6.	Aside from the experimental intervention, were the groups treated equally?	x		
B)	**What are the results?**			
7.	How large was the treatment effect?	70 laparoscopic cholecystectomy patients.		
8.	How precise was the estimate of the treatment effect?	Decrease of myalgia was statistically significant.		
C)	**Will the results help locally?**			
9.	Can the results be applied in your context? (or to the local population)	x		
10.	Were all clinically important outcomes considered?			x
11.	Are the benefits worth the harms and costs?	x		

Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist

Study 4: Vyankatesh, J.S., Kiran, T.V., & Satish, D.G. (2016). Comparative study of pretreatment with rocuronium and vecuronium in post succinylcholine fasciculation, intubation condition and myalgia. *Journal of Evolution of Medicine and Dental Sciences*, 5:38), 2319-2324.

A)	**Are the results of the trial valid?**	**Yes**	**Can't tell**	**No**
1.	Did the trial address a clearly focused issue?	x		
2.	Was the assignment of patients to treatments randomized?	x		
3.	Were all of the patients who entered the trial properly accounted for at its conclusion?	x		
4.	Were patients, health workers, and study personnel "blind" to treatment?	x		
5.	Were the groups similar at the start of the trial?	x		
6.	Aside from the experimental intervention, were the groups treated equally?	x		
B)	**What are the results?**			
7.	How large was the treatment effect?	150 adult patients undergoing elective surgery.		
8.	How precise was the estimate of the treatment effect?	Both Rocuronium and Vecuronium were efficacious and the decrease in myalgia was statistically significant with both drugs. However, Rocuronium was noted to be more efficacious as compared to Vecuronium.		
C)	**Will the results help locally?**			
9.	Can the results be applied in your context? (or to the local population)	x		
10.	Were all clinically important outcomes considered?	x		
11.	Are the benefits worth the harms and costs?	x		