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Review

Does adding muscle relaxant make post-operative pain better? a narrative review of the literature from US and European studies

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Centrally acting skeletal muscle relaxants (CASMR) are widely prescribed as adjuncts for acute and chronic pain. Given the recent interest in multimodal analgesia and reducing opioid consumption, there has been an increase in its use for perioperative/postoperative pain control. The mechanism of action, pharmacodynamics, and pharmacokinetics of these drugs vary. Their use has been studied in a wide range of operative and non-operative settings. The best evidence for the efficacy of CASMRs is in acute, nonoperative musculoskeletal pain and, in the operative setting, in patients undergoing total knee arthroplasty and abdominal surgery, including inguinal herniorrhaphy and hemorrhoidectomy. The risk of complications and side effects, coupled with the limited evidence of efficacy, should prompt careful consideration of individual patient circumstances when prescribing CASMRs as part of perioperative pain management strategies.

Keywords: Analgesics; Muscle; Muscle relaxant; Pain; Pain management; Substance-related disorders.

INTRODUCTION

Centrally acting skeletal muscle relaxants (CASMR) are well-studied and widely prescribed as adjuncts for acute and chronic pain. Given the recent interest in multimodal analgesia and reduction in opioid consumption, there has been an increase in their use for outpatient pain control [1]. However, no extensive literature is available on this prescription pattern. This review will cover the use of centrally acting muscle relaxants administered pre-, intra-, or post-operatively via any route other than neuraxial for the purpose of perioperative analgesia. This review will not cover muscle relaxants that work peripherally (such as dantrolene, rocuronium, or cisatracurium) or the use of benzodiazepines, which may mediate postoperative analgesia through other means. The goal of this review is to examine how CASMRs might reduce postoperative pain, describe clinical conditions (i.e., for which types of surgeries) where CASMRs might benefit patients, and describe the known risks including complications of CASMRs when used in conjunction with other medications commonly administered in the perioperative period.

We performed a literature search for the use of methocarbamol (Robaxin®, Pfizer, Canada), cyclobenzaprine (Flexeril® Merck Sharp & Dohme, USA), tizanidine (Zanaflex® Athena Neurosciences, USA), metaxalone (Skelaxin®, Core

Table 1. Centrally Acting Muscle Relaxants and Potential Site of Action

Drug [5]	Site of action
Baclofen	Binds to the GABA-B receptor and reduces release of excitatory neurotransmitters and substance P.
Cyclobenzaprine	Exact mechanism is unknown. Postulated to inhibit serotonergic descending systems in the spinal cord.
Metaxalone	Exact mechanism unknown. Speculated to be a general CNS depressant.
Methocarbamol	Exact mechanism unknown. Possibly inhibition of acetylcholinesterase at the synapse at autonomic nervous system, neuromuscular junction and CNS.
Orphenadrine	Exact mechanism unknown. Appears to block muscarinic acetylcholine receptors and NMDA receptors in the CNS
Tizanidine	Presynaptic alpha-2 agonist which directly impairs excitatory amino acid release from spinal interneurons.

GABA-B: G-protein coupled receptor for gamma-aminobutyric acid, NMDA: *N*-methyl-D-aspartic acid, CNS: central nervous system. All pharmacologic information can be found on Drugbank.com [5].

Pharma LLC, USA), baclofen (Lioresal®,Ciba, Switzerland), and orphenadrine as perioperative analgesics. Only English articles or abstracts were used. The content was then organized into categories describing the pharmacology, acute vs. chronic pain management, and type of surgery.

PHARMACOLOGY

Despite multiple comparative studies conducted since the 1950s, the exact mechanisms of many CASMRs remain unknown. Some animal studies have suggested that their effects may be due to the inhibition of interneuronal activity and blocking polysynaptic neurons in the spinal cord and descending reticular formation in the brain [2,3]. Other studies have suggested that depression of neuronal activity may be a consequence of their sedative effects [4]. Tizanidine has been shown to have an affinity for alpha-2 receptors in the central nervous system (CNS), which is presumed to be the primary mode of action of this drug (Table 1) [5].

PHARMACOKINETICS

Most CASMRs have an onset of approximately one hour. The duration varies from 4–6 h to as much to 24 h, depending on the specific agent. Owing to the similarities found in this class, as well as the unreported profiles of some of its constituents, a brief summary has been provided in table format (Table 2) [5].

Table 2. Onset of Action, Duration and Half-life of Central Acting Skeletal Muscle Relaxants

Drug [5]	Onset	Duration	Half-life
Baclofen	1–2 h	Not reported	5.5 h
Cyclobenzaprine	1 h	4–6 h	2–3 h
Metaxalone	30 min	Not reported	1–2 h
Methocarbamol	1 h	4-5 h	14 h
Orphenadrine	1 h	12–24 h	1–3 days
Tizanidine	0.75–2 h	6–8 h	2.1–4.2 h

All pharmacologic information can be found on Drugbank.com [5].

CLINICAL EFFICACY (NONOPERATIVE)

Low back pain, musculoskeletal disorders, and muscle spasm

Several trials have shown CASMRs to be more effective than placebos in treating acute painful musculoskeletal disorders and muscle spasms. One of the principal benefits is the shorter recovery time and ability of the patient to return to normal activities, including work, after only a few days [6-9]. Another benefit is the reduced likelihood of dependency and abuse compared with opioids, with the exception of carisoprodol [10]. Another common observation is that muscle relaxants generally have the greatest effect within the first week of low back pain (LBP) treatment [11]. After the first week, the pain-relieving effect appears to gradually decrease, suggesting that short-term treatment is most beneficial and may accelerate recovery [11]. Several studies have demonstrated that the combination of muscle relaxants with nonsteroidal anti- inflammatory drugs (NSAIDs) or analgesics can achieve a more rapid onset of pain relief than analgesics or NSAIDs alone [12,13]. Friedman et al. [14,15] demonstrated that CASMR combined with NSAIDs/analgesics was not significantly more effective in lowering pain levels. Both studies revealed that combination therapies did not provide more pain relief than single muscle relaxant therapies.

CASMR are commonly used in the treatment of acute LBP, a practice based on many studies demonstrating significant pain relief in this patient population [16,17].

As an extension of its use in LBP, other studies have exam-

ined the effects of CASMR on other forms of acute pain. Aljuhani et al. [16] examined the efficacy of muscle relaxants for nonspecific acute traumatic pain and found no benefit compared with those who did not receive methocarbamol. However, another study in patients with acute traumatic rib fractures demonstrated a significant reduction in cumulative opioid consumption in patients administered methocarbamol compared to a placebo [18]. Additionally, the use of CASMR in patients with rib fractures reduced the length of hospital stay.

Few studies have tested the treatment of chronic pain using CASMRs, and there is little evidence to support their use in this setting. Gouveia et al. [12] observed that subjects were primarily affected by CLBP and pain-relief treatments. They found that few patients used analgesics for pain, and within that small percentage, CASMRs were used less frequently than most other analgesics. Overall, research indicates that the use of centrally acting muscle relaxants has a significant beneficial effect in the treatment of certain forms of acute pain, principally acute LBP [7]; however, data on their use in patients with chronic pain are lacking.

CLINICAL EFFICACY (OPERATIVE)

As CASMRs have been used effectively in non-surgical patients with pain of musculoskeletal origin [19], there is anecdotal evidence of their migration to surgical pain. Our literature search revealed 12 randomized, blinded, prospective studies across a variety of surgical specialties in which CASMRs were tested for surgical pain (Table 3). Additionally, our literature search included several retrospective reviews and case reports describing the use of centrally acting muscle relaxants in postoperative pain management. The CASMRs studied were cyclobenzaprine, tizanidine, baclofen, metaxalone, and methocarbamol. Supporting data on post-operative pain are described based on various surgical populations studied.

BREAST SURGERY

A randomized controlled trial by Al Yafi et al. [20] assessed the effectiveness of cyclobenzaprine for postoperative pain control in patients undergoing subpectoral breast reconstruction. Stretching of the pectoralis major muscle during these procedures is associated with high levels of pain and muscle spasms. Despite the association with muscle spasms, there was no statistically significant reduction in pain scores or consumption of oral opioids in the cyclobenzaprine group at any point during the study.

In 1997, Schneider [21] reported observational data on methocarbamol use during breast augmentation surgery. On a subjective level, most patients (84%) felt that methocarbamol significantly improved their discomfort compared to opiates alone. Seventy-seven percent of the patients reported that they would select methocarbamol if only one medication could be selected for postoperative pain control.

Hidalgo and Pusic [22] studied methocarbamol and intercostal nerve blocks in bilateral submuscular breast augmentation surgery in a prospective randomized trial. The authors reported no significant differences in patient characteristics between the treatment groups that received methocarbamol and those that received an intercostal nerve block. Due to the lack of difference between pain scores by the visual analog scale (VAS) after 3 h, the authors concluded that postoperative muscle spasms, if present, subside significantly–2–3 h postoperatively.

SPINE SURGERY

As previously mentioned, muscle relaxants have been useful in treating acute back pain. Their utility in treating acute back pain has raised the possibility that they may also be useful in the treatment of acute postoperative back pain [23]. In 1954, Selvin [23] performed a study comparing use of Myanesin® (mephenesin) in patients with staged multiple spinal fusion surgeries. The results showed no appreciable difference in postoperative opioid consumption in the groups who did and did not receive Myanesin®.

Nielsen et al. [24] studied the effect of chlorzoxazone on acute post-operative pain in patients who underwent spinal surgery (cervical and lumbar discectomy, decompression, and fusion). The results showed no significant difference between the treatment and placebo groups regarding the primary endpoint of pain during mobilization. Additionally, there was no difference between the two groups when assessing pain at rest, pain during mobilization at any assessment time point, or the total use of morphine after the intervention. Ultimately, the authors could not recommend the use of chlorzoxazone for analgesia in acute postspinal surgery settings.

In 2019, Chin and Lewis [25] published a case report highlighting the possibility of opioid-free analgesia for posterior spinal fusion surgery using ultrasound-guided erector spinae plane (ESP) blocks and postoperative baclofen. In the

Table 3. Surgery Specific Studies Using Centrally Acting Muscle Relaxants and Their Conclusions

Region of the body	Surgery	Study type	CASMR studied	Conclusions	Author/year
Head	Craniotomy	Literature Review	Methocarbamol [29]	Multimodal analgesia with non-opioid Rx, regional anesthesia (scalp block) and CASMR advocated to reduce perioperative opioid use	Ban et al. 2019 [29]
	Removal affected 3rd molar	RCT*	Cyclobenzaprine [45]	No statistical difference in CASMR vs. non-CASMR groups for pain scores, trismus or need for supplemental analgesia	De Santana Santos et al. 2011 [45]
	Removal affected 3rd molar	RCT*	Orphenadrine Cyanocobalamin [57]	Statistically significant decrease VAS pain scores in CASMR group; no statistical decrease in acetaminophen consumption in CASMR group	Barroso et al. 2006 [57]
	Removal affected 3rd molar	RCT	Baclofen [58]	No statistical difference in CASMR vs. non-CASMR groups in time interval to initial opioid consumption	Gordon et al. 1995 [58]
	Removal affected 3rd molar	RCT	Tizanidine [44]	No statistical difference in CASMR vs. non-CASMR group for VAS pain scores	Kirmeier et al. 2007 [44]
	Thyroidectomy	RCT*	Tizanidine [42]	Statistically significant less postoperative cervical pain, headache opioid consumption in CASMR group vs. non-CASMR groups	Ahiskalioglu et al. 2018 [42]
Thorax	Breast Reconstruction	RCT	Cyclobenzaprine [20]	No statistical difference between CASMR vs. non-CASMR group	Al Yafi et al. 2021 [20]
	Breast augmentation	RCT	Methocarbamol [22]	No statistical difference in CASMR vs. non-CASMR group after 3 h opostoperative	Hidalgo and Pusic, 2005 [22]
	Breast augmentation	Observational	Methocarbamol [21]	Subjectively CASMR effective	Schneider, 1997 [21]
	Pectus	Retrospective review	Methocarbamol [46]	Patients in the multimodal analgesia protocol with CASMR had decreased hospital length of stay	Inge et al. 2003 [46]
Spine	Posterior spinal arthrodesis (pediatrics)	Retrospecive review	Cyclobenzaprine Methocarbamol [59]	Increase in CASMR prescriptions tied to decrease in opioid prescriptions	Harris et al. 2020 [59]
	Posterior spinal fusion	Case report	Baclofen [25]	Possible to deliver opioid-free anesthetic with erector spinae plane blocks, ketamine, dexmedetomidine, acetaminophen and baclofen	Chin and Lewis, 2019 [25]
	Cervical and lumbar discectomy/decompression/fusion	RCT	Chlorzoxazone [24]	No statistical difference in CASMR vs. non-CASMR group in reducing pain at rest or with mobilization, or total opioid consumption	Nielsen et al. 2016 [24]
	Spine surgery	RCT	Baclofen [26]	No statistical difference in CASMR vs. non-CASMR groups in opioid consumption POD 1–3 ; statistically significant reduction in muscle spasms in CASMR group POD 2–3	Blumenkopf, 1987 [26]
	Spine fusion	RCT	Myanesin [23]	No statistical difference in CASMR vs. non-CASMR group in postoperative opioid use	Selvin, 1954 [23]
Abdomen	Hemorrhoidectomy	RCT*	Baclofen [41]	Statistically significant lower VAS pain scores and analgesic consumption only at 1 and 2 weeks postop in CASMR group vs. non-CASMR group	Ala et al. 2020 [41]
	Inguinal hernia repair	RCT*	Tizanidine [37]	Statistically significant decrease in NRS pain scores from POD 0–4 at rest and with movement in CASMR group; CASMR group with longer interval to request supplemental analgesia; CASMR group with less overall use of supplemental oral analgesia	Yazicioğlu et al. 2016 [37]
	Major abdominal surgery	RCT	Orphenadrine [30]	Statistically significant longer interval to request supplemental analgesia in CASMR group	Fry, 1979 [30]
Limb	Total knee arthroplasty	RCT*	Epirisone [28]	Statistically significant decrease in VAS at rest and ambulation from POD 3 onwards in CASMR group better active ROM in CASMR group POD 3–14; less total morphine use in CASMR group	Gong et al. 2013 [28]

CASMR: centrally acting skeletal muscle relaxant, RCT: random control trial, VAS: visual analysis scale, POD: post-operative day, ROM: range of motion, *RCT, prospective, double blind.

case report, a 35-year-old female underwent revision T2–T8 posterior spinal fusion. The patient reported adequate analgesia without opioid use during surgery or postoperative hospital stay.

In 1987 Blumenkopf [26] did a single-blind, randomized, prospective study of 50 patients to assess the benefits of using antispasmodic agents (diazepam and baclofen) with meperidine versus a typical postoperative pain management regimen of meperidine alone. The overall results demonstrated no significant difference in opioid consumption on post-operative day 1, 2, and 3 between the two groups. However, there were significantly fewer reports of muscle spasms in group 2 on post-operative day two and three.

TOTAL KNEE ARTHROPLASTY

Johnson [27] and Gong et al. [28] hypothesized that adding a muscle relaxant, eperisone, to the postoperative pain management protocol would enhance analgesia by affecting the "spasm-pain-spasm" cycle. They predicted that less muscular spasm would lead to better analgesia and allow for enhanced postoperative rehabilitation, along with a better range of motion in the surgically repaired joint. The results were the same for all three groups on post-operative day 1. However, on post-operative days 3–14 group A (non-steroidal anti-inflammatory agent + celecoxib + eperisone) and B (non-steroidal anti-inflammatory agent only) had significantly reduced VAS scores compared with group C (placebo). Group A had a significantly better range of motion on post-operative days 3–14 compared to the other groups. Total morphine consumption was also the lowest in Group A.

CRANIOTOMY

In 2019, Ban et al. [29] published a literature review of multimodal pain management strategies for postoperative pain management after craniotomy. They recognized that opioids were fundamental to postoperative analgesia, but had some pitfalls, including excessive somnolence, nausea/vomiting, and hypoventilation/apnea. Because of these issues with opioid analgesia, a multimodal approach to post-craniotomy pain was advocated, including regional anesthesia (scalp blocks) and non-opioid pharmacies (*N*-methyl-D-aspartic acid antagonists, Gabapentinoids-pentinoids, Acetaminophen, NSAIDs, local anesthetics, central alpha blockers, and centrally acting skeletal muscle relaxers, such as methocarbamol).

MAJOR ABDOMINAL SURGERY

Orphenadrine is a muscarinic antagonist used specifically as a skeletal muscle relaxant without impairing normal muscle tone and voluntary movements. In 1979, Fry [30] demonstrated that patients who received orphenadrine had a significantly longer interval until the first request for analgesia than the control group.

HERNIA REPAIR SURGERY

Alpha-2 agonists such as dexmedetomidine and clonidine have been extensively studied for perioperative analgesia [31-33]. Tizanidine is a centrally acting alpha-2 agonist with muscle-relaxant, sedative, and anxiolytic properties. It has been used to treat pain associated with muscle spasms, and myofascial and neuropathic pain [34-36]. In 2016, Yazicioğlu et al. [37] studied tizanidine use after inguinal hernia repair in a randomized double-blind study. The primary objective was to assess the relative efficacy of tizanidine versus placebo in terms of pain scores, analgesic consumption, and time to return to daily routine. A numerical rating scale (NRS) was used to assess the pain management efficacy. The treatment group had significantly lower NRS pain scores at 6, 12, and 24 hours postoperatively, both at rest and during movement. This was also observed on post-operative days 1–4. The treatment group consumed less oral acetaminophen for breakthrough postoperative pain and had a longer median time to the initial request for supplemental oral analgesia than the control group.

HEMORRHOIDECTOMY

Topical baclofen has been reported to be effective in the treatment of neuropathic pain, especially when combined with other medications, such as amitriptyline and ketamine [38-40]. Ala et al. [41] studied topical baclofen 5% in a randomized double-blind placebo-controlled trial in patients undergoing open hemorrhoidectomy for 3rd and 4th degree hemorrhoids. The results showed significantly lower pain scores 1 and 2 weeks after surgery in the baclofen group. Additionally, the baclofen group consumed significantly fewer oral analgesics at weeks 1 and 2 than the placebo group.

THYROIDECTOMY

Ahiskalioglu et al. [42] examined a multimodal approach

for postoperative pain management in patients who underwent thyroidectomy. In a double-blind study, the administration of additional preoperative oral tizanidine reduced the incidence of posterior neck pain and occipital headache in the early postoperative phase.

DENTAL SURGERY

The removal of impacted mandibular third molars (M3) is associated with swelling, pain, and trismus. CASMR reduces muscular spasticity [43]. Kirmeier et al. [44] hypothesized that tizanidine aids in relaxing the muscles near the operative site of M3 extraction, leading to reduced trismus and pain. However, in that prospective trial, the authors could not recommend the addition of tizanidine to reduce trismus, pain, or facial swelling.

De Santana Santos et al. [45] aimed to evaluate the efficacy of cyclobenzaprine for M3 extraction. They conducted a prospective, randomized, double-blind, placebo-controlled study using a split-mouth design (the right and left sides of the mouth were randomly assigned to two treatment groups). There was no difference in the need for additional pain medication for breakthrough pain between the two groups.

PECTUS SURGERY

Inge et al. [46] reviewed patients undergoing surgical correction of pectus excavatum over a 42 month period. Postoperative hospital length of stay was lower in the minimally invasive group. The majority of pain during minimally invasive repair of the pectus was assumed to be triggered by the diffuse strain of the muscles of the anterior chest wall, which led the authors to favor the use of centrally acting muscle relaxers.

COMPLICATIONS

The most commonly reported adverse effects of CASMRs are sedation, dry mouth, fatigue, dizziness, and nausea. These side effects have raised concerns regarding their potential for abuse [47,48]. In a study by Gouveia et al. [12], they observed that patients taking opioids reported the worst quality of life followed by those patients taking CASMRs.

Strong evidence in support of CASMR in acute musculoskeletal pain has led to the broadening of its prescribing indications among practitioners [49,50]. Patients with acute or chronic pain are often prescribed muscle relaxants as adjuvants to NSAIDs and/or opioid regimens. The CNS-depressant effects of this drug class should prompt caution when prescribing them. One study by Golden et al. [51] suggested that patients with a mean age of 80 years were at an increased risk of fracture injuries. Their adjusted odds ratio of 1.40 was similar to the risk in those prescribed short-acting benzodiazepines (odds ratio 1.33). The odds ratio remained significant even after adjusting for the increased incidence of psychotropic medications and their diagnoses in this population. In another study by Spence et al. [52], patients with a mean age of 75 years had a 1.32 fold increased risk of injury when taking CASMR. The four most common injuries were fractures (30%), contusions (27%), falls (21%), and lacerations (13%). Sixty one percent of those injured were female.

Another limitation is the risk of abuse or overdosing. CNS depressant effects have been reported to potentiate the effects of opioids and benzodiazepines. Carisoprodol, a skeletal muscle relaxant, has been shown to bind to the non-benzodiazepine-binding site of GABA-A receptors in both in vivo and in vitro studies [53]. Owing to their synergistic activities, some authors have discouraged the concomitant use of benzodiazepines, CASMR, and opioids in standard practice [54,55]. A recent study by Li et al. [56] illustrates this risk. In their population-based cohort study, they generated an overdose hazard ratio of 1.21 (95% confidence interval, 1.00–1.48) when pooling both opioid naïve and chronic patients who were prescribed CASMR with opioids. A significant risk was noted in the 55–65 year age group and in those prescribed the opioid/CASMR combination for more than 14 days [57,59].

CONCLUSION

As previously mentioned, CASMRs are being prescribed more frequently in outpatient settings for pain relief. It is reasonable to postulate that increasing concerns about opioid epidemics do not mitigate this trend. Unfortunately, their safety and effectiveness have not been consistently demonstrated in high-quality studies. The best evidence of improved pain control is nonoperative acute musculoskeletal pain. In the perioperative setting, the best evidence of improved pain control is in patients undergoing total knee arthroplasty and abdominal surgery, including inguinal herniorrhaphy and hemorrhoidectomy. In these specific cases, randomized controlled trials have suggested that the use of CASMRs, such as tizanidine, may reduce pain scores, facili-

tate early ambulation, and reduce the overall use of other analgesics. Unfortunately, in the majority of the surgery types studied, including neck/spine, breast, and oral surgeries, the results did not show any benefits.

In addition to the limited effectiveness of CASMRs, their use increases the risk of injury, and may be accompanied by abuse. Considering their limited efficacy, side effects, abuse potential, and risk of injury, clinicians must carefully consider the use of CASMRs in the perioperative setting.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

Conceptualization: Ricardo Verdiner, Narjeet Khurmi, Christopher Choukalas, Colby Erickson, Karl Poterack. Data curation: Narjeet Khurmi, Colby Erickson. Formal analysis: Ricardo Verdiner, Christopher Choukalas. Methodology: Ricardo Verdiner, Narjeet Khurmi, Christopher Choukalas, Colby Erickson, Karl Poterack. Project administration: Ricardo Verdiner. Visualization: Ricardo Verdiner, Narjeet Khurmi. Writing - original draft: Ricardo Verdiner, Christopher Choukalas, Colby Erickson. Writing - review & editing: Ricardo Verdiner, Narjeet Khurmi, Christopher Choukalas, Colby Erickson, Karl Poterack. Investigation: Ricardo Verdiner, Narjeet Khurmi, Christopher Choukalas, Colby Erickson, Karl Poterack. Resources: Colby Erickson. Supervision: Ricardo Verdiner. Validation: Ricardo Verdiner, Narjeet Khurmi, Colby Erickson, Karl Poterack.

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