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MUSCLE RELAXANTS IN MULTIMODAL PAIN MANAGEMENT

SUMMARY

Muscle relaxants are a heterogeneous class of medications that act by different mechanisms. They may be broadly divided into antispastic and antispasmodic medications. In addition to having muscle relaxing properties, they may cause central nervous system side effects such as sedation, dizziness, etc... They have been used for many years for painful musculoskeletal conditions such as chronic low back pain. In recent years, they have been included in multimodal pain management strategies.

RECOMMENDATIONS

- **Level 1**
 - **None**
- **Level 2**
 - **Antispasmodic muscle relaxants are superior to placebo as single agents for pain control in conditions such as low back pain. They may lead to improved function as measured by range of motion exercises and return to activities of daily living. They may also lead to improved pain at rest and at night.**
- **Level 3**
 - **Antispasmodic muscle relaxants may have a benefit as part of a multimodal pain management strategy for some elective surgeries such as breast augmentation and laparoscopic cholecystectomy.**
 - **Antispasmodic medications may have a benefit as part of a multimodal pain management strategy in trauma patients, especially in patients with multiple rib fractures.**

INTRODUCTION

Muscle relaxants can be divided into 2 groups: antispastics and antispasmodics. Antispastics (baclofen, dantrolene) are prescribed for spastic neurologic conditions such as cerebral palsy and multiple sclerosis. There is no evidence that these agents are useful for acute painful musculoskeletal conditions and should not be used for such. Antispasmodic agents which are used for acute painful musculoskeletal conditions are divided into 2 groups: benzodiazepines and non-benzodiazepines. The non-benzodiazepines include cyclobenzaprine, tizanidine, carisoprodol, metaxalone, and methocarbamol among others (1,2). While the mechanism for most of these agents is unclear, they are all central nervous system depressants and their effect may be related to sedation. Cyclobenzoprine (flexeril) is related to tricyclic antidepressants. Methocarbamol (robaxin) is structurally similar to mephenisim, and while the mechanism of action is unknown, it is thought to cause inhibition of carbonic anhydrase and may interact with NMDA receptors. Tizanidine (zanaflex) is a centrally acting alpha-2 receptor agonist.

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

Antispasmodics have been utilized for quite some time in the treatment of acute musculoskeletal low back pain. These agents have gained recent popularity for inclusion in multimodal pain management strategies for treatment of acute pain despite the limited evidence demonstrating efficacy for these agents. The following review is of the agents used most frequently in multimodal pain management strategies.

LITERATURE REVIEW

Cyclobenzaprine

In 2001, Browning et al. evaluated cyclobenzaprine in the treatment of acute low back pain (3). This was a meta-analysis involving 14 randomized controlled trials. This meta-analysis found that compared to placebo, those patients given cyclobenzaprine were more likely to report improvement of symptoms at day 14 compared to those given placebo (Odds ratio 4.7, 95% CI 2.7-8.1). The treatment effect was modest (0.38-0.58) but was observable in all 5 investigated outcomes: local pain, muscle spasm, tenderness to palpation, range of motion, and activities of daily living. Efficacy was greatest in the first 3 days of treatment and declined over the next 1 to 2 weeks. The number needed to treat for 1 improvement was 3 patients. Adverse effects were more likely in the cyclobenzaprine group and included drowsiness, dizziness, and dry mouth. The authors noted that most of the studies included in the analysis had significant limitations including inadequate blinding, inadequate description of randomization, inadequate description of selection/inclusion criteria, etc... In 2003, Turturro et al. conducted a small randomized trial in patients presenting to the emergency department with minor trauma and acute musculoskeletal pain (4). In this trial, patients were randomized to ibuprofen plus cyclobenzaprine vs. ibuprofen alone for 48 hours following presentation. At no time throughout the study did the addition of cyclobenzaprine result in a significant improvement in reported pain score over ibuprofen alone. However, the cyclobenzaprine group did show an increase in central nervous adverse effects including sedation, light headedness, fatigue, and confusion. In 2015, Friedman et al. performed a randomized controlled trial in patients presenting to the emergency department with acute low back pain (5). All patients received naproxen and were randomized into 3 other protocols: placebo, cyclobenzaprine, and oxycodone/acetaminophen. Patients were treated as outpatients for one week and re-evaluated at the end of this period using the Roland Morris Disability Questionnaire (RMDQ). At one week follow up, the RMDQ improvement in the placebo group was 9.8, in the cyclobenzaprine group was 10.1, and in the oxycodone/acetaminophen group was 11.1. Between group difference in mean RMDQ improvement for cyclobenzaprine vs. placebo was 0.3 (98.3% CI, -2.6 to 3.2; p=0.77), for oxycodone/acetaminophen vs. placebo was 1.3 (98.3% CI, -1.5 to 4.1; p=0.28), and for oxycodone/acetaminophen vs. cyclobenzaprine was 0.9 (98.3% CI, -2.1 to 3.9; p=0.45). They concluded that among patients with acute low back pain, the addition of oxycodone/acetaminophen or cyclobenzaprine to naproxen did not improve pain scores or functional outcomes at 1 week post-injury.

Methocarbamol

Methocarbamol is one of the oldest antispasmodics having been in use since the 1950's. While the exact mechanism of action is unclear, it is thought to act within the spinal cord and inhibit muscle spasm without affecting the neuromuscular junction. In 1975, Tisdale performed a double blind randomized controlled trial of methocarbamol vs. placebo in patients with acute musculoskeletal pain and spasm from traumatic or inflammatory conditions (6). A total of 180 patients were randomized into either placebo or treatment groups. After 48 hours, they found that there was a significant advantage in the methocarbamol group compared to placebo. After 48 hours, 76.7% of methocarbamol patients reported improvement in local pain compared to 42.2% in the placebo group. Muscle spasm and limitation in motion was reported as improved in 75.6% and 72.2% compared to 43.3% and 56.7%. Finally, 81% of patients in the methocarbamol group reported that they would take the medication again for a similar condition compared to 47% of placebo patients. In 2005, Hidalgo et al. investigated the use of methocarbamol in a breast augmentation model (7). This trial was conducted in 2 phases. In the first phase, all patients received preoperative oral methocarbamol and were randomized to receive intercostal nerve blocks or no nerve blocks. In the second phase, patients did not receive any methocarbamol, but were still randomized to receive intercostal nerve blocks or no nerve blocks. This group found that whether or not a patient received intercostal nerve blocks had no impact on VAS pain scores, but use of methocarbamol was associated with lower VAS pain scores in the first 6 hours after surgery. There was no benefit beyond this time frame. Postoperative narcotic use

was not different among the 4 groups. In 2013, Looke et al. performed a retrospective review of 150 patients receiving primary hip and knee replacement surgery (8). These patients were given intravenous methocarbamol and acetaminophen in the preoperative area. These were compared to 150 historical controls who received preoperative oral analgesics including oral oxycodone, acetaminophen, and pregabalin. Compared to the group receiving preoperative oral analgesics, the group receiving IV acetaminophen and methocarbamol showed significantly less postoperative opioid use and improved physical therapy progress with increases in average and maximum walking distance. Finally, in 2015 Aljuhani et al. performed a retrospective matched cohort study of 100 patients receiving methocarbamol for 3 days following admission for traumatic injury (9). They found that there was no significant association between methocarbamol use and mean pain score on day 1 [coefficient 0.09, 95% confidence interval (CI), 20.57 to 0.75, $p = 0.782$, model $R^2 = 0.43$], day 2 (coefficient 0.47, 95% CI, 20.15 to 1.09, $p = 0.140$, model $R^2 = 0.42$), or day 3 (coefficient 0.51, 95% CI, 20.13 to 1.16, $p = 0.117$, model $R^2 = 0.42$) after injury. They concluded that methocarbamol did not improve pain control in the first 3 days of admission following traumatic injury.

Tizanidine

Tizanidine is a centrally acting alpha-2 adrenergic agonist. In 1988, there were 2 studies published by Hutchinson et al. investigating the use of tizanidine plus ibuprofen or aspirin. In the first, patients with acute low back pain were randomized to receive either ibuprofen plus tizanidine, or ibuprofen plus placebo (10). Pain was assessed at 3 and 7 days. It was found that both groups had effective treatment of symptoms, but patients receiving tizanidine reported earlier resolution of symptoms. There was a significant improvement in pain control in the tizanidine group compared to placebo especially in those patients with moderate to severe pain at night, at rest, and in those with severe sciatica. It was also noted that those patients taking tizanidine had significantly fewer gastrointestinal adverse events compared to those taking ibuprofen alone. In the second study, patients were randomized to receive either tizanidine or placebo (11). They were also given aspirin 300 mg to use as rescue medication. It was found that in the tizanidine group, the consumption of aspirin was half that compared to the placebo group. Pain at night, pain at rest, and restriction of movement were better controlled in the tizanidine group compared to placebo. It was again noted that there were fewer gastrointestinal adverse events in the tizanidine group compared to the placebo group. This is in keeping with animal model research showing that tizanidine mediates gastric mucosal protection against anti-inflammatory drugs. In 2009, Pareek et al. evaluated tizanidine in combination with aceclofenac (NSAID) vs. aceclofenac alone in the treatment of acute low back pain associated with radiographically proven degenerative lumbo-sacral spinal disorders (12). They found that adding tizanidine to the NSAID resulted in improved VAS pain scores, and decreased pain especially at rest and at night. They also noted increased spinal mobility in the tizanidine group. In September 2016, there was a small randomized controlled trial of 70 patients undergoing elective cholecystectomy. They were randomized to receive either tizanidine or placebo 90 minutes prior to surgery. In the tizanidine group, patients required much less postoperative narcotic medication and had shorter recovery room stay compared to placebo. Tizanidine associated adverse effects include hypotension, sedation, and dry mouth. It has also been associated with hepatotoxicity. Hepatic function should be checked, and it should be avoided in patients with impaired hepatic function. Withdrawal and rebound hypertension can occur; therefore, it should be tapered in those patients who have taken tizanidine for long periods of time.

Benzodiazepines

Benzodiazepines, such as diazepam, function as agonists of the GABA-activated chloride channel within the central nervous system. This results in sedation, anxiolysis, anticonvulsant, and muscle relaxing properties. As reported in a 2003 Cochrane database review, there have been several studies evaluating benzodiazepines in the management of acute and chronic low back pain (13). For acute low back pain, they reported limited evidence that benzodiazepine treatment was superior to placebo for short term pain relief, and better overall improvement, but it was noted that there were a substantial number of central nervous system side effects including dizziness, drowsiness, and confusion. In the treatment of chronic low back pain, there was strong evidence that benzodiazepines were more effective than placebo for short term pain relief and overall improvement compared to placebo (14). In direct comparison with other muscle relaxants, diazepam was found in one small high quality trial to be inferior to carisoprodol for treatment of muscle spasm. In a separate small, but high quality trial, diazepam was found to be equivalent to tizanidine for treatment of pain, muscle spasm, and functional status.

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