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A Review of Studies on the Use of New Non-Gabapentinoid Anticonvulsants and Muscle Relaxants in the Control of Acute Postoperative Pain

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ABSTRACT

Postoperative pain management in any type of surgery is an important issue for patients. The pain relief contributes to decreased hospital costs, shorter hospital stay, and elevated patient consent. Correspondingly, in this review article we assessed the postoperative pain management efficacy of new non-gabapentinoid anticonvulsants and muscle relaxant drugs in pre-clinical and clinical studies. The scientific databases, including PubMed, Embase, Scopus, and Google Scholar, were searched using relevant keywords: surgery, postoperative pain, analgesia, non-gabapentinoid anticonvulsants, and muscle relaxants. New anticonvulsants reduce postoperative pain, length of stay at postoperative anesthesia care unit, and analgesic requirement after surgeries. Their mechanisms include the inhibition of glutamate release, blocking the N-type calcium channels of afferent neurons, inhibition of supraspinal 5-hydroxytryptamine-3 receptor, and prevention of cyclin-dependent kinase 5-mediated collapsin response mediator protein 2 phosphorylation. Also, muscle relaxants show the same effects by downregulation the Cacna1a, Cacna1b, and Runt-related transcription factor 1 genes of dorsal root ganglia, inhibition the release of glutamate, aspartate or substance P from the terminals of primary afferent C and Aδ fibers, expression of Neurokinin 1 receptor in the spinal dorsal horn, agonistic effect on α2-adrenoceptor, and stimulation of acetylcholine release in the spinal cord. With respect to the concerns regarding opioid abuse, muscle relaxants and non-gabapentinoid anticonvulsant drugs can be regarded as a safe option for postoperative pain control.

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Introduction

Pain is a personal experience and is recognized as an emotional feeling or uncomfortable sensation in people as a result of physical or non-physical damages (1, 2). The most common reason to visit an emergency room is acute pain, and also surgical operations are related to acute postoperative pain induction (3).

Nociceptors such as thermoreceptor mechanics are activated by thermal, mechanical, and chemical stimulations, thereby mediating acute pain. Then, sensory neurons pass these sensations via various peripheral nerve fibers. In addition, the first part of the pain induced by Aδ-fibers is sharp and well localized, and the second part of the pain is poorly localized and steadily modulated by C fibers (4). These neurons result in neurogenic inflammation through the release of various substances to the periphery. Some of these proinflammatory neuropeptides are calcitonin gene-related peptide (CGRP) and substance P (SP), which contribute to the stimulation of immune cells, plasma extravasation, and vasodilation (5). Moreover, peripheral nerve terminals lead to sensitization of local tissues and surrounding afferent terminals by releasing glutamate and aspartate (6). Consequently, stimulating N-methyl-D-aspartate (NMDA) receptors cause an increase in excitability in the posterior horn neurons of the spinal cord and prolongation of postoperative pain.

Effective pain control promotes hemodynamic and metabolic stability, increases patient satisfaction, accelerates discharge from the hospital, reduces treatment costs, and affects the

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patient's recovery by preventing the progression of acute pain into chronic pain (7). Although opioid analgesics, local anesthetics, and Nonsteroidal anti-inflammatory drugs (NSAIDs) are often used to manage postoperative pain, many studies have been conducted to use other drug classes to improve the analgesic effect and reduce complications such as the risk of bleeding with NSAIDs or respiratory depression, apnea, nausea and vomiting of opioids and tolerance to them (2, 8).

Two classes of non-opioid drugs have been studied with relatively successful results to control acute postoperative pain in recent years. They include muscle relaxants such as baclofen, tizanidine, methocarbamol, and cyclobenzaprine, as well as new anticonvulsant drugs such as lacosamide, levetiracetam, lamotrigine, and topiramate. In this review article, we intended to evaluate the results and effectiveness of these drugs by reviewing the results of preclinical studies and clinical trials. Finally, we hope this study could improve the current knowledge about the use of new muscle relaxants and anticonvulsants to control acute pain after surgery while maintaining the benefits of conventional analgesics, improve their effectiveness, and reduce the incidence of side effects.

Methods

The data were collected by searching PubMed, Scopus, Google Scholar, and Embase databases. The searched keywords were: "preoperative", "perioperative", "postoperative", "post-surgery", "postsurgical", "post-surgical", "operation", "operative", "surgery", "surgical", "pain", "ache", "algesia", "hyperalgesia", "analgesia", "analgesic", "Lacosamide", "Lamotrigine", "Levetiracetam", "Topiramate", "Baclofen", "Cyclobenzaprine", "Methocarbamol", and "Tizanidine". The asterisk wildcard (*) was utilized to increase the search accuracy. Review articles, duplicate publications, and non-relevant articles were excluded. The search was limited to studies in the English language except for one study in the Spanish language that only the abstract was available and two Persian articles.

Results

Data collection was carried out by searching articles published from 1984 to September 2020, including animal studies and clinical trials that evaluated the efficacy of preoperative administration of non-gabapentoid anticonvulsants and muscle relaxants on acute postoperative pain. Eventually, 33 original articles related to the searched subject were selected for this narrative review.

Non-gabapentinoid anticonvulsants

Several clinical studies have revealed the efficacy of antiepileptic drugs such as pregabalin and gabapentin to control neuropathic pain and they are used as preemptive analgesics. Among the nine articles related to non-gabapentoid anticonvulsants for acute postoperative pain control, seven studies were performed on humans, often in the form of clinical trial study and the rest of them were animal and cellular studies. Five articles with a total number of 400 patients were related to lamotrigine which was more promising for postoperative pain control compared with other drugs. Also, each of the drugs lacosamide and levetiracetam had two related articles. Lacosamide had only one case report and levetiracetam was studied in a total of 120 patients. The previous researches on new anticonvulsants including lamotrigine, lacosamide, and levetiracetam to control postoperative pain were reviewed here.

Lamotrigine

One of the most significant points in pain control of patients is that lamotrigine plays a part in the control of central pain, trigeminal neuralgia, postherpetic neuralgia, and peripheral neuropathic pain. A study on 30 patients under cystoscopic prostatectomy indicated that administration of 200 mg lamotrigine orally 1 hour before spinal anesthesia caused a significant reduction of the need for diclofenac consumption as a rescue analgesic and visual analog scale (VAS) scores at 2,4 and 6 hours after surgery (9).

Three similar randomized placebo-control studies on 90 patients including major surgeries such as orthopedic or obstetrics-gynecology operations have shown that administration of 100 mg oral lamotrigine before anesthesia induction in comparison to 10 mg sugar tablet, 100 mg diclofenac sodium, 300 mg gabapentin, or 200 mg topiramate leads to a statistically significant reduction in pain score, postoperative analgesic assumption, and patient's discomfort, without remarkable side effect at least during 24 hours after surgery (10-12).

In another randomized controlled trial (RCT) study concerning the management of postoperative pain in impacted third molar surgery, 200 mg lamotrigine was administered 2 hours before the operation and the patients were observed for 12 hours to assessing the VAS score. Finally, they concluded that lamotrigine did not relieve pain compared with placebo. Maybe, one gap in this study was a small sample of participants (13).

Lacosamide

Lacosamide (LCM) is a third-generation anticonvulsant medication with sodium-channel (Nav1.7 and Nav1.3) blocking properties that have been approved to use in diabetic neuropathic pain. Moutal A. et al., in 2016 (14) performed animal and cellular (Isolated Sensory DRG neurons from Sprague-Dawley rats) studies regarding the evaluation of the (S)-LCM enantiomer of LCM efficacy and its mechanism on N-type voltage-gated calcium channel (CaV2.2). The results showed that LCM inhibits mechanical and thermal hypersensitivity as well as postsurgical and neuropathic pain.

In a case study, lacosamide had a successful therapeutic effect on a 36-year-old female with a history of allergy to gabapentin or pregabalin, who suffered from neuropathic pain because of brachial plexus surgery (15).

Levetiracetam

Levetiracetam as a piracetam structural analog is a second-generation antiepileptic drug with a broad spectrum (16). The results obtained by Das et al., (16) showed that the prescription of 500 mg levetiracetam 2 hours before laparoscopic cholecystectomy did not decrease rescue analgesic requirement and intensity of postoperative pain in patients. The score of acute postoperative pain has been assessed by VAS.

The purpose of the Sliva et al., study (17) was to determine the preemptive efficacy of levetiracetam (250, 500, and 1000 mg/kg) in a model of incisional surgery of the hind paw in rats. They measured the levetiracetam preemptive efficacy at 1 hour before induction of pain in the preoperative treated group or 1 hour after the induction of pain in the postoperative treated group. They determined this efficacy through thermal hyperalgesia calculated via the plantar test. The results of this investigation showed that pretreated animals with levetiracetam displayed remarkably elevated paw withdrawal latency in a dose-dependent manner. The second major finding was that post-incisional levetiracetam treatment could not develop an antihyperalgesic effect. So, they proposed levetiracetam as a preemptive analgesic drug.

The collected data regarding the efficacy of antiepileptic drugs in the management of postoperative pain are shown in Table 1.

Table 1. Summary of antiepileptic drugs studies for controlling postoperative pain.

References	Medication	Study population	Study design	Results
(9)	Lamotrigine	30 patients undergoing prostatectomy	1 h before spinal anesthesia Test: 200 mg lamotrigine p.o. Control: placebo	↓ VAS score at 2, 4, and 6 hours after the operation. ↓ Diclofenac consumption
(12)	Lamotrigine	90 patients undergoing orthopedic/ obstetrics-gynecology surgery	30 min before operation Test: 100 mg lamotrigine p.o. Standard: 100 mg of diclofenac sodium p.o. Control: 10 mg of sugar tablet	↓ VAS, FRS, and BRS scores ↓ PACU length of stay ↓ Analgesic requirement ↑ Patient comfort
(11)	Lamotrigine	90 patients undergoing orthopedic/ obstetrics-gynecology and surgery	30 min before operation Test 1: 200 mg Topiramate p.o. Test 2: 100 mg lamotrigine p.o. Control: 100 mg diclofenac sodium	↓ PACU length of stay ↓ analgesic requirement ↑ Patient comfort in the lamotrigine group compared to topiramate and control groups ↓ VAS till 4 h and FRS at 2 h in the lamotrigine group compared to the control group. The highest pain scores were observed in the topiramate group.
(10)	Lamotrigine	90 patients undergoing orthopedic/ obstetrics-gynecology Surgery	30 min before operation Test 1: 200 mg Topiramate p.o. Test 2: 100 mg lamotrigine p.o. Control: 300 mg Gabapentin	↓VAS and BRS at 2 h in lamotrigine group compared to topiramate and gabapentin groups. The highest analgesic requirement and pain scores at 1 h and 2 h after surgery were observed in the topiramate group.
(13)	Lamotrigine	100 eligible adult patients undergoing impacted third molar surgeries	Test: 200 mg lamotrigine p.o. Control: 20 cc water	No significant differences
(14)	Lacosamide	Incisional surgery in adult male Sprague-Dawley rats	Spinal administration of lacosamide 3μg/5μL	Inhibition of mechanical and thermal hypersensitivity. ↓ Postsurgical and neuropathic pain
		Isolated Sensory DRG neurons from Sprague-Dawley rats	Excitatory solution containing 200 μM, 20 μM, 2 μM, 200 nM, 20 nM, or 2 nM (S)-LCM	
(15)	Lacosamide	A 36-year-old female patient with neuropathic pain who is allergic to gabapentin and pregabalin	Patient treated with lacosamide	↓ Neuropathic pain with little adverse effects after brachial plexus surgery
(16)	Levetiracetam	120 patients undergoing laparoscopic cholecystectomy	2 hours before surgery Test: 500 mg levetiracetam p.o. Control: placebo	No differences in analgesic requirement and intensity of postoperative pain
(17)	Levetiracetam	Incisional surgery of the hind paw of 76 adult male Wistar albino rats	1 hour before surgery Control: saline 1 ml/kg i.p. Test1: 250 mg/kg levetiracetam i.p. Test2: 500 mg/kg levetiracetam i.p. Test3: 1000 mg/kg levetiracetam i.p. Test5: 5 mg/kg morphine i.p. Same doses administered 1 hour after surgery in 5 postoperative treated experimental groups	Preoperative treatment: ↑ PWL in all levetiracetam doses Postoperative treatment: ↓ PWL in all levetiracetam doses

p.o.: Orally (from the Latin "per os", by mouth), VAS: Visual Analog Scale, FRS: Facial Rating Scale, BRS: Behavioral Rating Scale, PACU: Postoperative Anesthesia Care Unit, i.p.: Intraperitoneal injection, PWL: Paw withdrawal latencies.

Muscle relaxants

Another class of drugs that have been clinically tested in postoperative pain control is muscle relaxants that relieve pain by reducing muscle spasms, especially in the early hours after surgery. From the articles published in this field, twenty-three articles were selected based on the criteria of this review article. Except for two animal studies, the rest of them were done mostly with a clinical trial study design on humans Among the studied muscle relaxants, tizanidine and methocarbamol had a total patient population of 612 in eleven studies and 463 in four studies, respectively. These two drugs were more promising among the studied muscle relaxants for postoperative pain control. The articles also contained seven clinical studies with 304 patients for baclofen and one study with 50 patients for cyclobenzaprine.

Baclofen

Baclofen is a skeletal muscle relaxant used to treat neuropathic pain and symptoms of spasticity from multiple sclerosis, spinal cord injury, and spastic diplegia (18).

It has appeared from the animal model of acute postoperative pain investigation that the combination of μ-theraphotoxin-Pn3a as a selective NaV1.7 inhibitor with Gamma-aminobutyric acid (GABA; GABAB) receptor agonist baclofen led to the synergistic antinociceptive effect of baclofen on Pn3a analgesic function. The score of post-surgery pain was assessed by hind paw withdrawal threshold and plantar skin incision tests. Based on the results, the transcriptome analysis showed the downregulation of Cacna1a (CaV2.1), Cacna1b (CaV2.2), and Runx1 (Runt-related transcription factor 1) genes of dorsal root ganglia in the designed mouse model (19).

Furthermore, the prescription of baclofen (0.3 or 0.6 mg/kg IV) and fentanyl (1.5 mg/kg IV) for abortion in female volunteers showed that baclofen notably improved postoperative pain management dose-dependently. It should be noted that baclofen in combination with fentanyl exhibited partially more potent analgesic effect than when the drug has prescribed alone (20).

Interestingly, an intrathecal baclofen pump in a 64-year-old woman with spastic diplegia who received hydrocodone as needed facilitated her physical therapy and left knee arthroplasty and also minimized opioid use requirement. The finding provided evidence that the continuous lumbar plexus infusion of baclofen is a successful and suitable therapy in management the of spasticity and perioperative pain (21).

For the reason, that muscle spasms and pain are important factors in postoperative complaints particularly in spinal surgery, in a clinical trial diazepam and baclofen as antispasmodic and pain control agents administered to 50 consecutive patients. The findings highlighted preoperatively decreased muscle spasm and pain on days 2 and 3 after the operation with diazepam and baclofen (22).

Diminished both acute and chronic verbal pain scale (VPS) until three months after total knee arthroplasty by addition of 100 mcg baclofen to standard spinal narcotic therapy confirmed that intrathecal baclofen could be considered as a beneficial postoperative pain adjuvant therapy which decreased the need for postoperative opioid administration. The clear benefits of preemptive intrathecal baclofen are induction of profound antinociception and impressive analgesia in any pain situation such as neuropathic pain (23).

Due to the effect of topical baclofen in neuropathic pain relief, Ala et al., (24) recently prescribed baclofen cream 5% to hospitalized patients who underwent open hemorrhoidectomy for diminishing the postoperative pain and continued the administration every 12 h for 14 days. Postoperative pain scores measured with VAS values showed significant differences between treatment and placebo groups from the first week onwards. Furthermore, the patients on baclofen did not need to use other analgesic medications. In summary, the study concluded that topical baclofen is a pain-relieving drug with successful results.

The only failed clinical trial was related to the administration of baclofen 3 mcg/kg bolus injection immediately before and 0.5 mcg/kg/ml continuous epidural infusion after the operation in children suffered from cerebral palsy who needed extremity surgery. In general, baclofen perfusion into the intrathecal space influences neurons. However, the result of the study was possibly due to insufficient intrathecal doses of baclofen to create clinical effects because of its high cost (25).

Methocarbamol

Methocarbamol is a central muscle relaxant and CNS depressant. However, the exact mechanism of action is unclear (26). Oral and intravenous administration of methocarbamol preoperatively showed that it can significantly improve postoperative care by reducing pain score, analgesic requirement, and patient discomfort. Due to its reasonable price and negligible adverse effect, it can be an optimal drug for controlling postoperative pain (27).

In one study, treatment with methocarbamol which is used to treat musculoskeletal pain was examined to reduce postoperative pain in breast augmentation. The researchers noted that administration of oral methocarbamol 1500 mg before the operation and 500 mg regularly every 6 hours in comparison to intercostal nerve blocks alone could lessen VAS pain score in the first few hours after breast augmentation by relaxing the pectoralis muscle. The study revealed that methocarbamol is a beneficial drug in relieving early perioperative pain with limited adverse effects such as sedation and nausea (27).

Similar findings were reported by Schindler et al., in two clinical trials which indicated that methocarbamol may be used in abdominoplasty, breast augmentation, and reconstruction as a part of pain relief treatment (26, 28). In one of these studies, 1500 mg methocarbamol was prescribed intravenously in the early period of surgery and continued with 750 mg orally four times daily (26). However, the other study was conducted by prescribing 1500 mg methocarbamol orally 30 minutes before the operation (28). Despite the different methods of administration of methocarbamol in two studies, the high usefulness of

methocarbamol in reducing pain, recovery time, and the need for intravenous narcotics were demonstrated. This benefit is justified by the effect of methocarbamol on relieving pectoralis muscle spasms (29).

The above finding is consistent with the study by Looke et al., (29), who established a retrospective cohort study and then indicated using intravenous methocarbamol and acetaminophen from 1 dose preoperatively to regular dosing for 48 initial hours, caused a reduction in opioid consumption, VAS pain score, and hospital discharge time in patients under the total hip and knee replacement. Importantly, it improved progress physiotherapy of knee bending along with mean and maximum walking distance.

Tizanidine

Tizanidine as an imidazoline derivative is a central α2 adrenergic agonist that has demonstrated to be clinically useful in chronic headache, neuropathic pain, and spasticity management in multiple sclerosis and spinal cord injury (30).

The aim of the Imanaga et al., study (31) was to evaluate the efficacy of premedication with tizanidine prior to surgery for decreasing infiltration pain in patients undergoing epidural catheterization. The findings indicated that the VAS score in the tizanidine group was significantly lower than the control group. This study found that tizanidine premedication is usually a safe intervention for relieving the infiltration pain in patients who required epidural catheterization for local anesthesia.

With the same objective, Talakoub et al., (32) performed a double-blinded clinical trial concerning postoperative pain management with tizanidine in patients undergoing elective laparoscopic cholecystectomy with general anesthesia. The study showed that receiving 4 mg tizanidine 90 minutes prior to the anesthesia induction led to a substantial decrease in the incidence of pain and analgesic requirement in surgery patients.

In one study, the postoperative pain control was done by the choice of tizanidine as an alpha-2 agonist with bilateral superficial cervical plexus block (BSCPB) in patients undergoing thyroidectomy. The data of the study including opioid use, posterior neck pain, Surgical Pain Scales (SPS), and rescue analgesia were obtained from patients at 24 hours' time points. The most important clinically relevant finding was the relief of postoperative pain and posterior neck pain, as well as decreasing the need for postoperative opioid utilization by the combination of single-dose tizanidine and ultrasound-guided BSCPB (33).

Following the administration of oral tizanidine before tetracaine spinal anesthesia in gynecological patients, the prolongation in tetracaine spinal anesthesia was observed. Altogether, these results provided important insights into the use of tizanidine as a premedication before surgeries (34).

In a clinical trial planned by Yazicoglu et al., (35) single 4mg dose of oral tizanidine one hour before herniorrhaphy and then twice daily in the first week after surgery was useful. Tizanidine not only completely reduced the incidence of extreme pain in the test group, but also substantially decreased the times and amount needed for paracetamol administration in situations where the numerical rating scale (NRS) score was at least 4. Of note, pain control enabled patients suffering from herniorrhaphy to spend less time at rest and enhanced their quality of life and physical health.

The initial objective of a prospective clinical study was to identify the impact of tizanidine on pain, trismus, and swelling in patients undergo third-molar surgery. The beneficial effects of 4 mg tizanidine administered before third-molar surgery were limited to improve mouth opening ability in the early days after surgery. However, it was unclear to the investigators whether the observed effect was due to the analgesic function of tizanidine or its muscle relaxation property (36).

In patients undergoing anorectal surgery, administration of 4 mg oral tizanidine 1 hour before spinal anesthesia delayed the onset of pain and substantially decreased the severity of pain and the need for rescue analgesia (37).

A clinical trial carried out by Vatankhah et al., in 2017 (38) showed that taking 4 mg oral tizanidine 60 minutes before the induction of anesthesia for herniorrhaphy can meaningfully reduce both the mean pain intensity and the patient's need for Meperidine without affecting diastolic blood pressure and heart rate. Therefore, it can be considered as an effective premedication to control postoperative pain in those without any contraindications.

The evaluation of tizanidine efficacy on prolongation of spinal anesthesia-induced by lidocaine showed that its preoperative administration significantly increased the patient's anesthesia time and relaxation without any different side effects or changes in the hemodynamic status compared to placebo. Also, the study indicated that tizanidine as a α2 adrenoreceptor agonist, unlike clonidine, does not increase the risk of hypotension and sympatholytic events of local anesthetics. So, it was concluded that further studies with different methods of tizanidine administration are highly recommended (39).

Despite prior evidences, the prescription of oral tizanidine prior to the operation in patients undergoing septoplasty did not yield expected statistically significant results. Pain intensity data based on VAS score were measured and recorded four, and eight hours and in the morning after surgery. Researchers suggested that the efficacy of tizanidine in postoperative pain management may be related to the type and location of the surgery (30).

Of note, as observed from an animal study systemic tizanidine reduced postoperative pain and mechanical allodynia due to mechanical stimulation by its dose-dependent antinociceptive effect. The researchers proposed intraspinal prescription of tizanidine for control of postoperative pain instead of systemic administration due to non-sedation effects (40).

Cyclobenzaprine

Cyclobenzaprine is a skeletal muscle relaxant that has an antidepressant effect in high doses. It is used to relieve muscle disorders, fibromyalgia, and headache. However, Cyclobenzaprine administration in a clinical study on 50

patients undergoing third molar extraction did not improve pain, swallowing ability, and trismus. In addition, the drug led to mild somnolence and xerostomia (41).

The studies on the effectiveness of muscle relaxant medications in the treatment of postoperative pain are summarized in Table 2.

Table 2. summary of studies on muscle relaxants for controlling postoperative pain.

References	Medication	Study population	Study design	Results
(19)	Baclofen	Incisional hind paw surgery on adult male C57BL/6J mice models	Test 1: Pn3a 3 mg/kg i.p. Test 2: baclofen 3 mg/kg i.p. nociceptive response 15 minutes after prescription on a temperature-controlled metal surface was evaluated	Baclofen had a synergistic effect with opioid analgesics
(20)	Baclofen	83 women under elective abortion	Test 1: baclofen 0.3 mg/kg i.v. Test 2: baclofen 0.6 mg/kg i.v. Test 3: baclofen 0.3 mg/kg i.v. + fentanyl 1.5 mg i.v. Test 4: baclofen 0.3 mg/kg i.v. + diazepam 5 mg p.o. and 5 mg i.v. Control: placebo	↑ Analgesic effect of baclofen especially in higher doses or in combination with fentanyl
(21)	Baclofen	A 64-year-old woman with Spastic Diplegia under arthroplasty	7.5 mg hydrocodone QID PRN + intrathecal baclofen pump	↓Analgesic consumption Acceleration in physical therapy
(22)	Baclofen	50 patients undergoing spinal surgery	Test: Standard therapy + diazepam 5 mg p.o. TID + baclofen 5 mg on day 1, 7.5 mg on day 2, 10 mg on day 3 p.o. TID Control: standard therapy	↓ Pain ↓ Incisional muscle spasm ↑ Adaptive pain response
(23)	Baclofen	60 patient under knee arthroplasty	Test: standard therapy +100 mcg baclofen IT Control: standard therapy + saline	↓ VAS in 48-72 hours and 3 months after the operation ↓ Analgesic consumption
(24)	Baclofen	66 patient undergoing open hemorrhoidectomy	Test: baclofen 5% cream immediately and every 12 h for 2 weeks after surgery Control: placebo	↓ Pain score from week 1 ↓ Average analgesic consumption from week 1
(25)	Baclofen	44 children with cerebral palsy under orthopedic surgery	Test: standard therapy + baclofen 3 mcg/kg bolus immediately before surgery and 0.5 mcg/kg/ml epidural infusion after operation Control: standard therapy	No significant difference in the analgesic requirement, pain score, and duration of hospitalization
(27)	Methocarbamol	100 patient undergoing breast augmentation	Test 1: 1500 mg methocarbamol p.o. preoperation and 500 mg p.o QID + intercostal nerve blocks Test 2: 1500 mg methocarbamol i.v. during surgery + 750 mg p.o QID Test 3: intercostal nerve blocks Control: neither methocarbamol nor intercostal nerve blocks	↓ VAS pain score in the early hours after the operation No difference in narcotic requirement
(26)	Methocarbamol	62 Women Undergoing subpectoral breast implant surgery	1500 mg methocarbamol i.v. during surgery + 750 mg p.o. QID	↓ Typical instantaneous pain ↓ Narcotic requirement ↓ Time to stay in the recovery room ↑ Patient function and comfort
(28)	Methocarbamol	Women undergoing subpectoral breast implant surgery	1500 mg methocarbamol p.o. 30 minutes preoperation	↓ Typical immediate pain ↓ Narcotic requirement ↓ Duration of stay in the recovery room ↑ Patient function and comfort ↓ Postoperative morbidity
(29)	Methocarbamol	Total hip and knee replacement operation in 300 patients	Test: 2011 protocol (1 dose i.v. methocarbamol and i.v. acetaminophen preoperatively and methocarbamol p.o. 500 mg TID for the first 48 hours after the operation) Control: 2008 protocol (celecoxib + oxycodone-acetaminophen p.o. pre and postoperatively)	↓ Opioid consumption ↓ Duration of hospitalization ↓ VAS pain score Accelerate in physical therapy

Table 2. Continued.

References	Medication	Study population	Study design	Results
(31)	Tizanidine	Epidural catheterization in 40 patients	Test: 3 mg tizanidine p.o. 1 hour before the operation Control: placebo 1 hour before the operation	↓ VAS pain score ↓ Blood pressure ↑ Drowsiness
(32)	Tizanidine	Laparoscopic cholecystectomy in 70 patients	Test: 4 mg tizanidine with 50 cc water p.o. 90 minutes before anesthesia Control: 50 cc water p.o. 90 minutes before anesthesia	↓ VAS pain score ↓ Opioid requirement ↓ Blood pressure in the first 30 minutes after surgery ↓ Time to stay in the recovery room
(33)	Tizanidine	Thyroidectomy in 60 patients	45 minutes before surgery Test1: BSCPB+ 0.25% bupivacaine+ oral placebo Test2: BSCPB+ 0.25% bupivacaine+ 6 mg tizanidine capsule Control: BSCPB+ 0.9% saline+ oral placebo	↓ Opioid consumption in the first 4 hours after surgery ↓Occipital headache and posterior back pain
(34)	Tizanidine	Tetracaine spinal anesthesia in 63 gynecological patients	Test 1: 0.25 mg of oral triazolam Test 2: 3 mg of oral tizanidine Test 3: 0.15 mg of oral clonidine (+13 mg tetracaine intrathecally in 2.6 ml glucose solution 10 %) Test 4: 0.25 mg of oral triazolam Test 5: 3 mg of oral tizanidine Test 6: 0.15 mg of oral clonidine (+13 mg tetracaine intrathecally in 2.6 ml of glucose solution 10% which contained 0.65 mg phenylephrine)	↑ duration of Tetracaine spinal anesthesia ↑ Time to start pain ↑ Time to need analgesics
(35)	Tizanidine	Inguinal hernia repair in 60 patients under general anesthesia	Test: 4 mg tizanidine p.o. Control: placebo pill (1 hour before surgery and twice daily in the first week after surgery)	↓ NRS at rest and during movement ↓ Paracetamol consumption ↑ Time to the first analgesic requirement Elimination of severe pain ↑ Ability to return to daily activities
(36)	Tizanidine	Third molar surgery in 48 patients	Test: 4 mg tizanidine p.o. QD Control: placebo (In the first 2 days after the operation)	↑ Mouth-opening ability on day 1 and 3 No significant difference in pain intensity and severity of edema
(37)	Tizanidine	Anorectal surgery in 60 male patients	Test: 4 mg tizanidine p.o. Control: Placebo tablet (1 hour before spinal anesthesia)	Delay to the onset of pain ↓ Rescue analgesia requirement
(38)	Tizanidine	100 patients undergoing herniorrhaphy	Test: 4 mg tizanidine in 50 cc water p.o. Control: 50 cc normal saline p.o. (1 hour before surgery)	↓ Average pain intensity ↓ Analgesic requirement ↓ Arterial O2 saturation
(39)	Tizanidine	40 male patient undergoing leg surgery	Test: 4 mg tizanidine p.o. Control: placebo (1 hour before spinal anesthesia)	↑ 10-15 minutes in spinal anesthesia ↑ Patient relaxation ↓ Sedative requirement
(30)	Tizanidine	Septoplasty in 71 patients	Test: 4 mg tizanidine p.o. Control: 100 mg Vit B1 (2 hours before surgery)	↑ VAS pain score after 4 hours No significant differences in VAS pain score 8 and 24 hours after surgery
(40)	Tizanidine	Incisional surgery to the hind paw of 60 rats	1 mg/kg tizanidine i.p. 30 minutes before surgery	↓ Pain score
(41)	Cyclobenzaprine	Third molar surgery in 50 patients	Test: 10 mg cyclobenzaprine QD Control: placebo (One day before and after surgery and the day of surgery)	No significant difference in pain, trismus, opioid consumption, swallowing ability, and duration of surgery Sedation and xerostomia were observed

p.o.: Orally (from the Latin "per os", by mouth), i.p.: Intraperitoneal injection, i.v.: Intravenous administration, IT: Intretheacal, VAS: Visual Analog Scale, NRS: Numeric Rating Scale, BSCPB: Bilateral superficial cervical plexus block.

Discussion

The effectiveness of muscle relaxants and new non-gabapentinoid anticonvulsant drugs was evaluated by statistical comparison of various factors, including the hospital length of stay, the ability to perform daily activities, the need for rescue analgesia, the prevalence and severity of complications, and most importantly, the pain score based on two parameters, VAS and NRS.

Most anticonvulsant drugs are used for various pharmacological aims. The mechanisms of anticonvulsants are important in the management of postoperative pain (42). In the following, we evaluate the related mechanism of new anticonvulsants in management the postoperative pain.

Glutamate is a factor in abnormal neuronal excitability leading to chronic and acute pain. Accordingly, lamotrigine could be considered as a preemptive analgesic by inhibition of glutamate release and antagonizing the glutamate-mediated excitatory neurotransmission (9). According to the successful administration of lamotrigine in fibromyalgia, trigeminal neuralgia, and chronic neuropathic pain and its efficiency in animal models, performing clinical trials to evaluate preemptive administration of lamotrigine preoperatively to decrease postoperative acute pain has been developed. Lamotrigine is a phenyltriazine antiepileptic drug that acts in three main ways, blockade of the voltage-mediated sodium channel in the central and peripheral nervous systems (CNS and PNS), inhibition of glutamate stimulatory effect, and increment in GABA transmission (2, 12). Consequently, due to presynaptic neuronal membrane stabilization, the release of glutamate as an excitatory neurotransmitter is inhibited, and thereby the sustained repetitive neuronal firing is prevented. Furthermore, lamotrigine possesses an inhibitory effect on supraspinal 5-hydroxytryptamine-3 (5-HT3) receptors of nociception which highlighted its antinociceptive potential (10-12). The reviewed articles showed us that lamotrigine is an effective drug for the reduction in pain score, postoperative analgesic assumption, and an enhancement in patient's discomfort.

The (S)-LCM enantiomer of LCM diminished neuropathy by inhibition of cyclin-dependent kinase 5 (Cdk5)-mediated collapsin response mediator protein 2 (CRMP2) phosphorylation and decrease in calcium entry in sensory neurons which confirmed by cellular and animal study done by Moutal A. et al., (14). CRMP2 that exists in the distal end of the dendritic spines can manage the size of the synaptic button. (S)-LCM is also a CaV2.2 blockers and inhibits the CRMP2-dependent neurite outgrowth. This property along with the prevention of CRMP2 phosphorylation via Cdk5 resulted in blocking the positive CRMP2 input to dendritic spine development thereby displayed its antagonism effects on chronic pain. Therefore, (S)-LCM could be considered as antinociceptive medication for neuropathic and postsurgical pain (14). We concluded that LCM possesses an effective role in the control of chronic pain in clinical and preclinical studies. However, further clinical researches are required.

Levetiracetam works via reducing neurotransmitter's presynaptic release by binding to a synaptic vesicle protein 2A (SV2A) and then blocking the calcium channels. Although its mechanism of analgesic effect is unclear, it may be related to action on opioids, GABAA, α2 adrenergic, and 5HT receptors (16). Both studies concerning the evaluation of levetiracetam efficacy on pain did not show acceptable beneficial analgesic effects in patients and rats.

In the following, we assess the previously published researches on muscle relaxants and related mechanism in the control of postoperative pain.

Baclofen is a GABA derivative that binds to the GABAB receptors. As a result, baclofen decreases calcium entry to the presynaptic terminal and causes muscle relaxation (18). The antinociceptive mechanism of baclofen may be related to the inhibition of neurotransmitters secretion such as glutamate, substance P, and CGRP from primary afferent fibers (24). In fact, baclofen exhibited an anti-nociceptive effect by prevention of the glutamate release from the terminals of primary afferent C and Aδ fibers and also inhibition of Neurokinin 1 (NK1) receptor expression in the spinal dorsal horn (24). Except in one case (an elderly woman), baclofen has exerted beneficial analgesic effects to reduce postoperative pain and analgesic consumption.

Although methocarbamol known as a drug for relieving muscle spasms and musculoskeletal pain, its precise mechanism is undisclosed (43). Anticholinergic inhibition of midbrain reticular is one of the suggested mechanisms that lead to depression of polysynaptic reflexes and reduction in muscle tone. This mechanism indirectly inhibits the interneuronal junction of the spinal cord. Importantly, methocarbamol does not exert a direct effect on motor nerve end plate, motor nerve fiber, and skeletal muscle contractility (44). Methocarbamol with preventive effects of postoperative pain has been relatively effective in reducing pain and increasing patient comfort.

Tizanidine is a central α2 adrenergic agonist that decreases secretion of excitatory amino acids, such as glutamate and aspartate in presynaptic spinal neurons resulting in muscle relaxation, nociceptive transmission modification, and preemptive analgesic activity (35, 45). The mechanism of tizanidine antinociceptive effects which affirmed by several animal and clinical studies may be related to stimulated releasing of acetylcholine in the posterior horn neurons of the spinal cord (37). As a α2 adrenoceptor agonist, tizanidine, along with a decrease in the need for volatile anesthetics and opioids, reduced the response to stress and pain during surgery (31). Tizanidine possesses beneficial effects regarding reducing pain intensity and analgesia after surgery and increasing the patient's comfort.

Although it is suggested that cyclobenzaprine as a muscle relaxant exerts beneficial effects in relieving postoperative pain, it could not decrease the pain, and opioid consumption in patients.

Conclusion

Acute postoperative pain is a common complication after any surgery. In recent years many attempts have been made to manage it. Regarding opioid-related dependence and side effects, the researchers are searching about the efficacy of

other drugs in postoperative pain management. In general, we could say that non-gabapentoid anticonvulsants with appropriate mechanisms such as inhibition of glutamate release, antagonizing the glutamate-mediated excitatory neurotransmission, blocking the N-type calcium channels of the dorsal horn and synaptic site of afferent neurons, inhibition of supraspinal 5-HT3 receptor, and prevention of CRMP2 phosphorylation exert antagonistic effects on postoperative pain, PACU length of stay, and analgesic requirement after surgeries. Furthermore, muscle relaxants downregulate the CaV2.1, CaV2.2, and Runx1 genes of dorsal root ganglia. They contribute to the control of postoperative pain through inhibition of the release of glutamate, aspartate or substance P from the terminals of primary afferent C and Aδ fibers, expression of NK1 receptor in the spinal dorsal horn, agonistic effect on α2-adrenoceptor, and stimulation of acetylcholine release in the spinal cord. However, Future clinical studies with large sample sizes are required to confirm the effects of these drugs on postoperative pain control.

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