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The Effect of Pregabalin on the Prevention of Succinylcholine-Induced Fasciculation and Myalgia

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A B S T R A C T

Purpose: This study evaluates the effect of pregabalin on fasciculation and myalgia after using succinylcholine.
Design: This randomized double-blind prospective study was conducted among 100 patients aged 20 to 60 years old.
Methods: Pregabalin (300 mg) and placebo (in capsule form) were placed in similar containers. The results were analyzed by SPSS 23 software, and statistical analysis consisted of χ^2 test and *t* test, and a *P* value less than .05 was considered significant.
Findings: The mean pain score in the group receiving pregabalin was lower than the placebo group. According to the χ^2 test, there was a significant difference between the two groups in the frequency of fasciculation ($P = .003$). Mean fasciculation severity in the pregabalin group was lower than placebo group. According to *t* test, there was a significant difference in the mean fasciculation severity between the two groups ($P = .002$).
Conclusions: This study showed that 300 mg of pregabalin was effective in reducing postoperative fasciculation and myalgia in patients treated with succinylcholine.

Succinylcholine is the only depolarizing muscle relaxant and possesses unique properties with quick onset and short duration of action, which is why it has been suggested as the first choice in rapid-onset anesthesia with adequate muscle relaxation.[1,2] The deep and sufficient muscle block provided by this drug creates a very good condition for intubation.[2] Succinylcholine is rapidly hydrolyzed by plasma cholinesterase, which is synthesized in the liver and present in plasma. Originally, the mechanism of succinylcholine-induced myalgia was unknown, but many mechanisms including increased myoplasmic calcium concentrations, degradation of membrane phospholipids, release of free fatty acids, and free radicals are thought to be causative factors.[2,3] One of the most important complications associated with succinylcholine use is postoperative pain and muscle cramp, which may last for several days and cause severe discomfort in patients.[3,4]

The incidence of myalgia after using succinylcholine has been reported to be between 0.2% and 89%.[5] Myalgia is more common in women, and it is more commonly treated in an ambulatory surgery setting than an inpatient hospital setting.[6] Myalgia is probably the result of the prejunctional action of succinylcholine, stimulating acetylcholine (ACh) receptors on the motor nerve, causing repetitive firing and release of neurotransmitter. In a meta-analysis that included 52 randomized trials with 5,318 patients, the incidence of fasciculation was 95%, and the incidence of myalgia at 24 hours was 50%.[7] Myalgia was more reduced when treated with 1.5 mg/kg succinylcholine than 1 mg/kg succinylcholine.[7] It has been shown that pretreatment with a prostaglandin inhibitor, such as lysine acetylsalicylate, is effective in reducing the incidence of succinylcholine-induced myalgia.[8] These findings suggest the possible role of prostaglandin and cyclooxygenase on succinylcholine-induced myalgia. Some researchers report myalgia even when they do not use succinylcholine.[9]

Conflict of interest: None to report.

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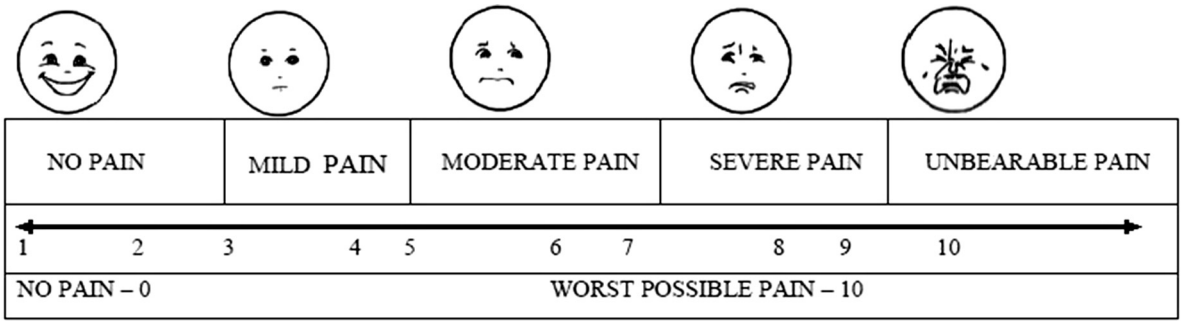

Figure 1. VAS score.

Different pretreatments have been used to reduce the incidence and severity of myalgia. Lidocaine,[10] benzodiazepines,[4] phenytoin,[11] ketorolac,[12] diclofenac,[13] vitamin C,[14] remifentanil,[15] gabapentin,[16] and magnesium sulfate[17] have been used, each demonstrating a certain level of success. It has been shown that pregabalin, similar to gabapentin, is effective in the improvement of neuropathic pain, postoperative pain, inflammatory pain, and formalin-induced damage.[18] Studies have shown that low-dose pregabalin is comparable with gabapentin in relieving the pain.[19]

Pregabalin is an anticonvulsant drug that has been shown to be effective in the treatment of central and peripheral neuropathic pain, including diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, and central neuropathic pain with spinal cord injury.[20] Because of the rapid onset of action, pain is usually reduced in adults on the first day after treatment with a multiple dose of 200 mg/d.[21] Three mechanisms for pregabalin are described: potentiation of gamma-aminobutyric acid transmission, reduction of glutamate-mediated excitatory transmission, and blockade of voltage-activated ion channels. Pain is reduced through the decrease of calcium influx into the intrafusal muscle fibers.[3] The most common complications of pregabalin include dizziness, drowsiness, and more uncommonly shaking, restlessness, memory disorders, limb edema, weight gain, and dysarthria.[22] This study evaluates the effect of pregabalin on fasciculation and myalgia after using succinylcholine.

Method

After being approved by the Research and Ethics Committee (IR.UMSU.REC.1395.308) of the Urmia University of Medical Sciences and Iranian Registry of Clinical Trials (IRCTID: IRCT20160430027677N11), this randomized double-blind prospective study was conducted among 100 patients (50 patients in each group). By using the specific sample size formula for determining the sample size to compare two proportions, based on the incidence of myalgia in the study by Srivastava et al,[23] and with considering the 80% power test and 95% confidence interval, the sample size of 42 people in each group was determined. Considering a dropout risk of 20%, we enrolled 50 patients in each group.

$$n = \frac{\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2 [P_1(1-P_1) + P_2(1-P_2)]}{(P_1 - P_2)^2}$$

Inclusion Criteria

Inclusion criteria include the following: patients with body mass index of 25 kg/m^2 and less, patients without any common chronic disease, aged 20 to 60 years old, American Society of Anesthesiologists class I and II, and patients have signed the consent form to participate in the study and scheduled for laparoscopic cholecystectomy.

Exclusion Criteria

Patients with body mass index greater than 25 kg/m^2, history of central nervous system disease, renal dysfunction, history of allergy to any of the drugs used during the study, history of peptic ulcer disease and antacid therapy, and patients who used an analgesic drug within 24 hours before surgery, or used any kind of sedative drugs were excluded from the study. Also patients with a history of taking antidepressants and calcium channel blockers, patients who had a contraindication for succinylcholine, and patients whose laparoscopic cholecystectomy was replaced with open cholecystectomy were excluded.

All patients were visited by the anesthesiologist the day before surgery. Adequate explanation and equal training were given to patients about the visual analog scale (VAS) (0—no pain and 10—the worst pain ever experienced) (Figure 1) in the anesthesia clinical examination room. Pregabalin (300 mg) and placebo (in capsule form) were placed in similar containers and were administered by the nurse 1.5 hours before the transfer to the operating room according to random number table, and the anesthesiologist and staff did not know which patient belonged to which group. The method of allocating participants into two groups was based on a random number table. In the operating room, a standard pulse oximetry monitor, noninvasive blood pressure measurement system, and an electrocardiogram were connected. After insertion of an 18-cm venous catheter, 1 mcg/kg body weight (mcg/kg BW) of fentanyl and 1 mg of midazolam were injected as premedication. Anesthesia was initiated through injection of 2 to 2.5 mg/kg BW propofol and 1.5 mg/kg BW succinylcholine. Anesthesia technique was the same for all participants. The incidence of fasciculation was evaluated and recorded, and orotracheal intubation was then performed. The scoring method for fasciculation was as follows: zero = without fasciculation; one = fasciculation in the eyes, neck, and face, or fingers without movement of the limbs; two = bilateral fasciculation or visible movements of limbs; and three = generalized and continuous severe fasciculation.[23] Anesthesia continued by isoflurane with oxygen and nitrous oxide (50% each) and atracurium

Table 1
Demographic Characteristics of the Study Population in the Two Groups

Variable	PG	P	*P*
Gender, *n* (%)			
Male	38 (76)	31 (62)	.09
Female	12 (24)	19 (38)	
Mean age (y)	46.43 ± 13.02	48.56 ± 10.11	.4
BMI (kg/m^2)	23.50 ± 3.04	24.33 ± 2.18	.06

PG, pregabalin group; P, placebo group; BMI, body mass index.

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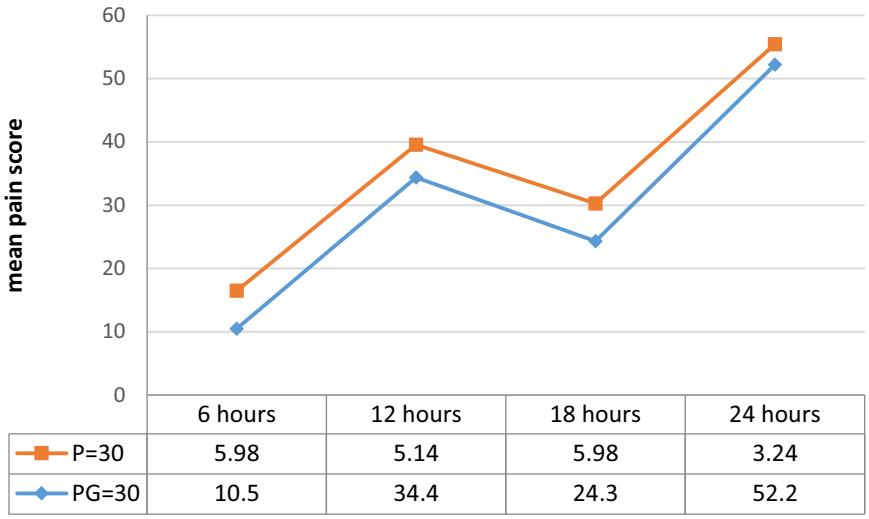

Figure 2. Comparison of pain score 6, 12, 18, and 24 hours fasciculation severity in the two groups. P, placebo group; PG, pregabalin group. This figure is available in color online at www.jopan.org.

besylate with repeated doses of 0.1 mg and 1 mcg/kg BW fentanyl. After the operation, progressive muscle relaxation was reversed with 0.04 mg/kg BW neostigmine and 0.02 mg/kg BW atropine. After assuring the patient's ability to protect the airway and spontaneous breathing, the patient's tracheal tube was removed. The patient was then transferred to the postanesthesia care unit. The incidence and severity of myalgia were measured at 6, 12, 18, and 24 hours after surgery (zero = no myalgia; one = muscle stiffness and pain related to one region; two = muscle stiffness and pain that is spontaneously expressed by the patient and may require an analgesic; and three = diffuse muscle pain with unbearable discomfort.[23] The postoperative pain scores were evaluated by the VAS scoring system and were recorded and analyzed using SPSS 23 software (IBM, Armonk, NY). Statistical analysis consisted of χ^2 test and paired Student *t* test. A *P* value less than .05 was considered significant (Figure 1).

Results

In this study, 100 patients undergoing cholecystectomy with general anesthesia and using depolarizing muscle relaxant of succinylcholine were divided into two equal groups. χ^2 and *t* Tests showed that the two groups were not statistically different in terms of demographic parameters (Table 1).

The mean pain score in the group receiving pregabalin was significantly lower than the placebo group (Figure 2; Table 2).

Frequency of succinylcholine-induced fasciculation included 34 people (68%) in the PG group and 46 people (92%) in the P group (Table 3), with a significant difference between the two groups in the frequency of fasciculation ($P = .003$).

Of 50 patients in the PG group, 16 patients (32%) had no fasciculation, 20 patients (40%) had fasciculation in the eyes and face, neck and fingers without limb movement, and 14 patients (28%) had observable bilateral fasciculation in the limbs (Figure 3; Table 4).

Of 50 patients in the P group, 4 patients (8%) had no fasciculation, 22 patients (44%) had fasciculation in the eyes, face, neck, and fingers without limb movement, and 23 patients (46%) had observable bilateral fasciculation in the limbs, and one person (2%) had severe generalized fasciculation, with a significant difference in the severity of fasciculation between the two groups ($P = .01$) (Figure 3; Table 4).

Mean fasciculation severity in the PG group was 0.96 ± 0.78 and placebo group was 1.42 ± 0.67 (Figure 4). The confidence interval was wide, and shows that the dispersion is high. Or it may be due to small sample size, so conducting more studies with big sample sizes is recommended. A T-test showed a significant difference in the mean fasciculation severity between the two groups ($P = .002$).

Discussion

This study was carried out during 1.5-year period in operating room A of Imam Khomeini Hospital among 100 patients aged 20 to 60 years, who were candidates for elective cholecystectomy with general anesthesia. For anesthesia, the depolarizing muscle relaxant succinylcholine was used for muscle relaxation and ease of intubation. Succinylcholine is the best choice for rapid muscle relaxation for intubation. Unfortunately, the use of this drug subsequently leads to fasciculation and myalgia. The fasciculation caused by this drug is associated with the activation of prejunctional depolarization, and as a result, repetitive stimulation of the neuromotor endings and uncoordinated discharges, followed by uncontrolled muscle contractions.[23] Various drugs have been used

Table 2
Comparison of Pain Score 6, 12, 18, and 24 Hours After Surgery in the Two Groups

Variable (h)	P ($n = 30$)	PG ($n = 30$)	*P*
6	10.5 ± 1.31	5.98 ± 1.02	.01
12	34.4 ± 1.58	5.14 ± 1.30	.007
18	24.3 ± 1.62	5.98 ± 1.02	.02
24	52.2 ± 1.47	3.24 ± 1.80	.03

P, placebo group; PG, pregabalin group.

Table 3
Frequency Distribution of Succinylcholine-Induced Fasciculation in the Two Groups

Group	Fasciculation, *n* (%)		Total, *N* (%)
	Yes	No	
PG	34 (68)	16 (32)	50 (100)
P	46 (92)	4 (8)	50 (100)
Total	80 (80)	20 (20)	100 (100)
P	.003		

PG, pregabalin group; P, placebo group.

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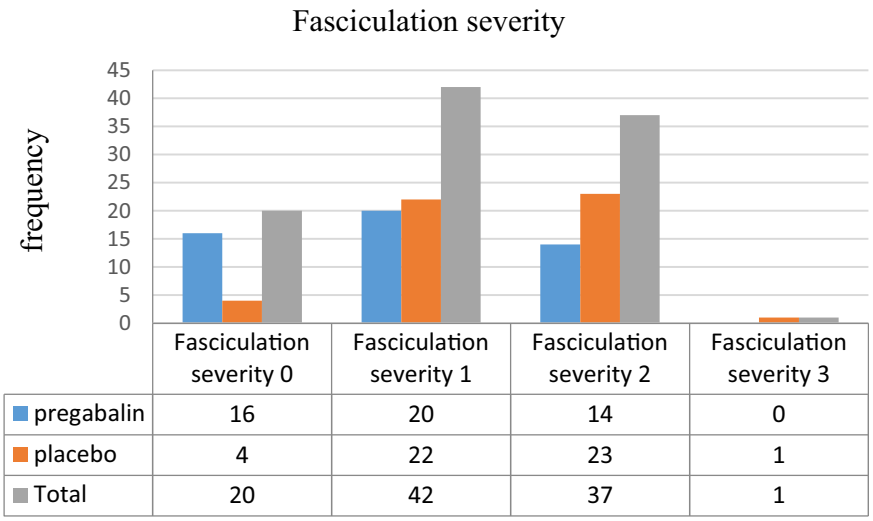

Figure 3. Distribution of fasciculation severity. Zero = without fasciculation, one = fasciculation in the eyes, neck, and face, or fingers without movement of the limbs, two = bilateral fasciculation or visible movements of limbs, and three = generalized and continuous severe fasciculation. This figure is available in color online at www.jopan.org.

to influence the incidence and severity of fasciculation, including morphine and nalorphine to reduce ACh release; the use of morphine to reduce neurohumoral transfer in muscarinic receptors,[15] the use of diphenylhydantoin to stabilize the motor neuron membrane through calcium ion reduction,[23] reduction of ACh release, followed by calcium ion reduction using magnesium,[17] and use of diazepam (1 mg/kg) or lidocaine (1.5 mg/kg) can decrease fasciculations and also prevent elevated blood pressure and heart rate during intubation.[24] The effect of inhibition of succinylcholine-induced fasciculation is not completely known. However, as previously mentioned, intracellular calcium accumulation is a major contributor to muscle contractions, and it seems that inhibition of calcium ion-dependent exocytosis can explain the effect of reducing muscle contractions that lead to fasciculation.[25]

Postoperative succinylcholine-induced myalgia is a common and annoying problem. The higher incidence of this complication occurs up to 1 day after the operation. The mechanism of muscle pain is not precisely defined. Various theories have been mentioned in this regard, including increased myoplasmic calcium concentration, decreased membrane phospholipids, the release of fatty acids and free radicals that cause muscle damage and subsequently myalgia.[23]

The present study showed that the incidence of fasciculation and its severity decreased after using pregabalin compared with placebo, and the difference was statistically significant ($P = .003$ and .01, respectively). Furthermore, the mean pain score and its severity in PG groups were statistically lower than the P group at 6, 12, 18, and 24 hours after surgery. The use of pregabalin seems to be effective in reducing the incidence and severity of this complication.

Table 4
Distribution of Fasciculation Severity in the Two Groups

Group	Fasciculation Severity, *n* (%)			
	0	1	2	3
PG	16 (32)	20 (40)	14 (28)	0 (0)
P	4 (8)	22 (44)	23 (46)	1 (2)
Total	20 (20)	42 (42)	37 (37)	1 (1)
P	.01			

PG, pregabalin group; P, placebo group.

In a study by Srivastava et al[23] to determine the effect of pregabalin on the prevention of succinylcholine-induced fasciculation and myalgia, they found that the use of 150 mg of pregabalin reduced the severity of succinylcholine-induced fasciculation and myalgia, although its incidence was not affected. The difference between this study and our study was in the incidence of fasciculation, which was lower in our study and was statistically significant. The dose we used in our study was 300 mg, which may explain the difference between the two studies.

A study by Pandey et al[26] evaluated the effect of pregabalin, gabapentin, and diclofenac on the incidence and severity of succinylcholine-induced myalgia and concluded that pretreatment with pregabalin, gabapentin, and diclofenac have equal effects on the incidence and severity of succinylcholine-induced myalgia. In addition, pretreatment with pregabalin and gabapentin reduces the postoperative pain score, which is consistent with our study results. We compared the effect of pregabalin with placebo, and the severity of pain and mean pain score was lower in patients of the PG group.

Another study by Pandey et al[16] evaluated the pretreatment effect of gabapentin on the incidence of succinylcholine-induced fasciculation and myalgia in laparoscopic cholecystectomy surgery. The result showed a decrease in the incidence and severity of

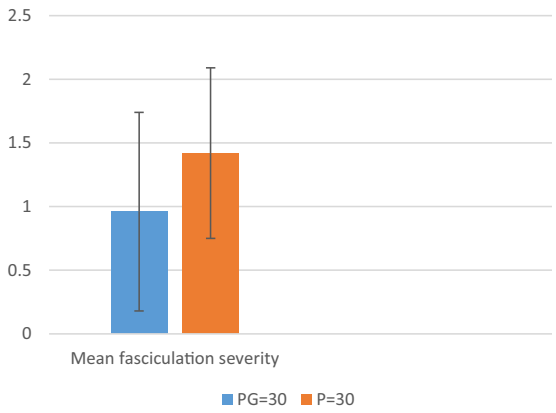

Figure 4. Fasciculation severity in the two groups. This figure is available in color online at www.jopan.org.

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myalgia and opioid use (fentanyl) for postoperative analgesia in the gabapentin group. We used pregabalin in our study and obtained similar results. The mechanism of the effect of these two drugs, that is, affecting calcium ion channels, is mentioned similarly for both of these drugs.

In a study that compared the effects of high-dose propofol on succinylcholine-induced fasciculations and myalgia by Kararmaz et al,[2] patients were divided into three groups: group 1 (thiopentone 5 mg kg), group 2 (propofol 2 mg/kg), and group 3 (propofol 3.5 mg/kg). Their study showed that the administration of propofol 3.5 mg/kg was effective in reducing fasciculations and myalgia after succinylcholine. In the present study, we used propofol with dose 2 mg/kg, and it is not a contributing factor and does not cause bias or deviation on incidence and severity of fasciculation and myalgia. Because all patients in the two groups were anesthetized by the same dose of propofol (2 mg/kg), the only factor that affected fasciculations and myalgia was using pregabalin.

Park et al[27] evaluated the effectiveness of pretreatment with 300 mg of pregabalin on postoperative analgesia in tonsillectomy compared with placebo and found that this drug can reduce postoperative pain. Pain reduction caused by pregabalin in the present study can also be due to its effect on the incidence of fasciculation and its analgesic effects.

Mathiesen et al[28] evaluated the effect of pregabalin and dexamethasone on postoperative pain in tonsillectomy and found that compared to 4 mg of diazepam, 300 mg of pregabalin before tonsillectomy reduced the use of fentanyl before surgery without increasing side effects. Mishra et al[29] conducted a study to evaluate the effect of oral gabapentin and pregabalin on postoperative analgesia in patients undergoing laparoscopic cholecystectomy with general anesthesia. This study showed that the PG group, compared with gabapentin group, had less request for longer analgesia, lower opioid, and lower VAS score. Similar results were obtained in our study, with the difference that we did not investigate the length and amount of analgesia request because our goal was to evaluate the pain caused by the incidence of the fasciculation, not the amount of pain at the operation site.

Conclusion

This study showed that compared with placebo, 300 mg of pregabalin was effective in reducing postoperative fasciculation and myalgia in patients treated with succinylcholine. Based on the studies mentioned previously and their comparison with the results of the present research, it seems that the use of these drugs at different doses and in more diverse surgical procedures can provide a good way to reduce the pain caused by succinylcholine-induced fasciculation.

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