



# A randomized controlled study on prevention of succinylcholine induced fasciculation and myalgia by pretreatment with pregabalin in patients undergoing laparoscopic cholecystectomy

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## ABSTRACT

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**Introduction:** Fasciculation and myalgia are the two most common and distressing side effects of succinylcholine administration. Many drugs have been tried to prevent or reduce this unpleasant happening with variable success. In this comparative study, we evaluated the preventive effect of pregabalin on the occurrence of succinylcholine induced fasciculation and myalgia in patients undergoing laparoscopic cholecystectomy.

**Methodology:** This, randomized controlled trial, was done in operating rooms of a teaching hospital over a period of six months. 70 patients of either sex, of ASA physical status 1 & 2, electively scheduled for laparoscopic cholecystectomy, were recruited for the study. Selected patients were divided into two groups with 35 patients in each group by lottery method of randomization. Study group - Group P received 150 mg of pregabalin orally two hours before anesthesia and Group C (control group) received placebo pills two hours before induction. Standard general anesthesia technique with succinylcholine as muscle relaxant at induction was used in all patients and incidence and severity of fasciculation at induction and postoperative myalgia were recorded in these patients.

**Results:** All the patients completed the study. Incidence of fasciculation was not significantly lower in pregabalin group ( $p$  value 0.096). However, its severity was significantly reduced in Group P as compared to Group C (1 vs. 7 patients). Incidence and severity of postoperative myalgia was quite reduced in Group P vs. Group C ( $p$  value 0.000).

**Conclusion:** Pretreatment with 150 mg of pregabalin two hours before anesthesia decreases the severity of succinylcholine induced fasciculation and reduces the incidence and severity of myalgia in patients undergoing laparoscopic cholecystectomy.

**Key words:** Succinylcholine; Fasciculation; Myalgia; Pregabalin; Laparoscopic cholecystectomy

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## INTRODUCTION

Succinylcholine has been a commonly used muscle relaxant for endotracheal intubation of surgical patients as it acts rapidly and has a short duration of action.<sup>1</sup> It has been associated with a number of side effects e.g. fasciculation and postoperative myalgia, bradycardia, hyperkalemia and malignant hyperthermia. However, fasciculation immediately after induction of anesthesia and subsequent myalgia in postoperative period outnumber the rest.<sup>2-4</sup> These side effects are very distressing for the patients especially for day case patients because postoperative myalgia may delay their discharge from the hospital. Different drugs have been tried to prevent the fasciculation as these are considered to be the real cause of postoperative myalgia. The different drugs used are atracurium, dexmedetomidine, benzodiazepines, magnesium sulphate, opioids and non-steroidal anti-inflammatory agents. Prior administration of small dose of lidocaine has been also used.<sup>5-14</sup> These drugs have been proven to have variable and limited success rate. An antiepileptic agent - gabapentin, has also been used to prevent succinylcholine induced fasciculation and myalgia in a double blind randomized controlled trial.<sup>15</sup> Another related antiepileptic drug, pregabalin was tried recently in a different clinical study to reduce the incidence and severity of fasciculation and myalgia in patients of spine surgeries.<sup>16</sup> These antiepileptics exert their action by potentiating the inhibitory effects of neurotransmitter gamma aminobutyric acid (GABA) and inhibit release of calcium ions inside the muscle cells and neurons.<sup>17</sup> The two drugs, gabapentin and pregabalin, have also been used successfully as analgesics for treatment of acute and chronic pain in some trials.<sup>18-21</sup> So in this study, our primary aim was to evaluate inhibitory effects of pregabalin on succinylcholine induced fasciculation and postoperative myalgia in our local population and in a different set of patients. We hypothesized that preoperative use of pregabalin two hours before anesthesia would decrease frequency and severity of succinylcholine-induced fasciculation and myalgia in patients undergoing laparoscopic cholecystectomy as compared to those patients who did not receive it.

## METHODOLOGY

This prospective, randomized, controlled study was carried out in operating room complex of a tertiary care hospital. Approval for study was obtained from the institutional review board and after written informed consent of patients, 70 patients of either sex, aged 22-65 years with ASA physical status I & II,

scheduled for elective laparoscopic cholecystectomy under general anesthesia were included in the study. Patients with history of hypersensitivity to any drug, history of seizures, hypertension, diabetes mellitus, impaired kidney or liver functions, increased intracranial and intraocular pressure were excluded from study. Pregnant or breast-feeding females and patients on antiepileptics, antidepressants and calcium channel blockers were also not included. The recruited patients were randomly allocated to one of the two equal groups of 35 patients each. Lottery method of randomization was used. Patients of Group P (pregabalin group) received 150 mg of pregabalin orally with a sip of water two hours before the induction of anesthesia. All patients in Group C (control group) received placebo pills two hours before the induction of anesthesia. All the patients were premedicated with oral midazolam 7.5 mg night before and two hours before operation. Standardized general anesthetic technique was used for the patients of both groups. In operating room, after establishing the basic monitoring of pulse, blood pressure, pulse oximetry and end tidal CO<sub>2</sub> capnography, anesthesia was induced by intravenous injection of nalbuphine 0.15 mg/kg, Propofol 1.5-2.0 mg/kg and succinylcholine 1.5 mg/kg body weight.

The intensity of fasciculation was assessed and recorded by a resident doctor who was blinded to the treatment groups of the patient and were graded as follows;

0 - (No fasciculation)

1- Mild (fine fasciculation at the eyes, neck, face or fingers without limb movement)

2- Moderate (fasciculation on both sides and obvious limb movement)

3- Severe (widespread, sustained fasciculation)

All information was noted in a specific proforma.

Patients were intubated using appropriate sized endotracheal tubes. Anesthesia was maintained with isoflurane 0.6 - 1.0% in oxygen and nitrous oxide at flow of 3 L/min. After the effect of succinylcholine was over, the muscle relaxation was maintained using atracurium 0.5 mg/kg body weight. Ringer's lactate was used as intravenous fluid for deficit and maintenance according to body weight. Intermittent boluses of 10 mg of atracurium were administered during surgery. On skin stitches, isoflurane was switched off. After return of two twitches on train of four (TOF), neostigmine 2.5 mg and glycopyrrolate 0.4 mg was administered intravenously for complete

reversal of neuromuscular block. Nitrous oxide was stopped, and the patients were extubated when fully awake. After extubation, patients were transferred to postanesthesia care unit (PACU). For postoperative pain, patients were treated with nalbuphine 0.05 mg/kg IV every two hours by assessing pain score on visual analogue scale. The first postoperative dose of nalbuphine was given two hours after surgery. The incidence and severity of myalgia was assessed by a resident doctor who was blinded of the groups, 24 hours after surgery and was graded as follows;

0 - No muscle pain

1 - Mild (muscle stiffness or pain on one area only but no treatment required)

2 - Moderate (muscle pain or stiffness indicated by the patient himself and treatment required)

3 - Severe (generalize, severe pain requiring more treatment)

**Statistical analysis:** Sample size was calculated on the basis of results found in previous studies, where fasciculation were recorded in 96% of the patients.<sup>15,16</sup> A samples size of 62 was calculated by considering 96% incidence of fasciculation, 7% level of precision, 5% level of significance and 80% power of study. Total 70 patients were enrolled in the study and they were equally allocated to each group. Statistical analysis was performed using the SPSS 22 statistical software. Independent variables were age, sex and weight of the patient while incidence and intensity of fasciculation and postoperative myalgia were recorded as dependent

variables. Quantitative data were expressed as mean and standard deviation while qualitative data were expressed as frequencies and percentages; incidence and severity of fasciculation and myalgia was analyzed using Chi square test. A p-value of < 0.05 was considered statistically significant.

## RESULTS

All seventy recruited patients completed the study. There were 21 (30%) male and 49 (70%) female patients (Table 1). The mean age of patients was  $43.18 \pm 8.97$  y with a range of 22 to 65 y. The mean weight was  $78.14 \pm 9.89$  kg (Table 1).

The fasciculations were absent in 3 (4.3%) patients of control and Group P each. Mild fasciculation were seen in 10 (14.3%) patients of Group C and in 17 (24.3%) patients of Group P. These were moderate in 15 (21.4%) patients of Group C and in 14 (20%) patients of Group P. Severe fasciculation were recorded in 7 (10%) patients of Group C and in 1 (1.4%) patient of Group P. The incidence of fasciculation between two groups was not significant ( $p = 0.096$ ). However, 7 patients suffered from severe fasciculation in the Group C compared to only one patient in Group P indicating that pregabalin reduced the severe fasciculation (Table 2).

The results of postoperative myalgia indicated that it was not recorded in 2 (2.9%) and 11 (15.7%) patients of control and Group P respectively. However, it was mild in 10 (14.3%) patients of Group C and in 19 (27.1%) patients of Group P. It was moderate in 18 (25.7%) patients of Group C and in 5 (7.1%) patients of Group P. Severe postoperative myalgia was present in 5 (7.1%) patients of Group C and none of the patient in pregabalin group experienced severe myalgia in postoperative period. The results were highly significant between two groups ( $p = 0.000$ ) (Table 3).

**Table 1: Demographic data**

Variable	Mean $\pm$ SD	Range
Age (years)	$43.18 \pm 8.97$	22-65
Weight (kg)	$78.14 \pm 9.89$	59-100
Male ; Female	3 : 10	

**Table 2: Incidence and severity of fasciculation in groups (Chi- Square test)**

Group	Incidence of fasciculation –n(%)				p-value
	Absent	Mild	Moderate	Severe	
Control	3(4.3)	10(14.3)	15(21.4)	7(10)	0.096
Pregabalin	3(4.3)	17(24.3)	14(20)	1(1.4)	

**Table 3: Incidence and severity of postoperative myalgia in groups (Chi- Square test)**

Group	Incidence of post-operative myalgia–n (%)				p-value
	Absent	Mild	Moderate	Severe	
Control	2 (2.9)	10 (14.3)	18 (25.7)	5 (7.1)	0.096
Pregabalin	11 (15.7)	19 (27.1)	5 (7.1)	0	

## DISCUSSION

Succinylcholine is a quaternary ammonium depolarizing muscle relaxant. It produces sustained depolarization of prejunctional membrane of neuromuscular junction without repolarization resulting in initially fasciculation followed by muscle relaxation.<sup>11</sup> It has rapid onset of action and short duration of action.<sup>1</sup> It provides

ideal intubation conditions and it is a drug of choice for short day case procedures requiring tracheal intubation.<sup>22</sup> However, these advantages of succinylcholine are compromised because of fasciculations produced by it as these fasciculations are considered to be the cause of postoperative myalgia in these patients. Exact mechanism of succinylcholine induced myalgia is still unknown. However, according to some proposed mechanisms, sustained muscle contractions (fasciculation's) cause increased calcium ion concentration in cytoplasm of muscle cells and cause degradation of cell membrane phospholipid resulting in increased release of free fatty acids and free radicals. These free fatty acids and free radicals actually cause muscle injury resulting in postoperative myalgia.<sup>3,4,14</sup>

There are some non-depolarizing muscle relaxants which have comparable speed of onset of action but have longer duration of action. Due to this, they are not suitable for short surgical procedures.<sup>22</sup> It has been reported in trials that incidence of succinylcholine induced myalgia is 41-92%<sup>23</sup> and it is commonly seen in first 24 hours of anesthesia in day case surgery.<sup>24</sup> Due to this reason we planned our study in patients undergoing for laparoscopic cholecystectomy as these patients recover rapidly from effects of surgery and anesthesia and become mobile early.

In various studies, different agents have been tried to decrease the frequency and intensity of these fasciculations and myalgia.<sup>5-12</sup> Fatemeh et al. demonstrated that pretreatment with atracurium decreases the incidence and severity of fasciculation but it has no beneficial effect on postoperative myalgia.<sup>25</sup> Different intravenous induction agents like propofol, thiopentone and benzodiazepines have been studied for their effects on fasciculation and myalgia but it was found that these agents had no effect on fasciculation and little effect on myalgia.<sup>13</sup> Maddineni et al. showed that propofol and thiopentone had same effects on postoperative myalgia.<sup>3</sup> Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to be beneficial in reducing the postoperative myalgia due to their analgesic property without having any effect on fasciculation.<sup>9</sup> This indicates that postoperative

myalgia might be due to an inflammatory process induced by succinylcholine and prostaglandins might be involved in it.

Antiepileptics, e.g. gabapentin and pregabalin also have been tried to prevent succinylcholine induced fasciculation and myalgia in different studies and these drugs also have shown analgesic effects on postoperative pain. In one study, gabapentin was used to show that it had significant effect on succinylcholine induced myalgia but its effect on fasciculation were similar in both study and control groups. The patients in the gabapentin group had lower incidence of myalgia (15/35) compared to the control group (24/35) with p-value 0.03.<sup>26</sup> In another study, pregabalin was used in patients of spine surgeries which showed that incidence of fasciculation was not significant between placebo and drug group ( $p = 0.707$ ). However, severity was significantly reduced in Group P ( $p = 0.028$ ). Similarly postoperative myalgia was significantly less in Group P vs. control group ( $p < 0.05$ ).<sup>16</sup> We also used same dose of pregabalin in this study for demonstration of same effects but in different setting and in different patients group undergoing laparoscopic cholecystectomy and our results are comparable with this study. In our study, preoperative use of pregabalin had not shown significant inhibitory effect on incidence of fasciculation as p value was 0.096 but it decreased the severity of fasciculations. However, incidence and severity of postoperative myalgia was significantly decreased in Group P as compared to Group C with p value of 0.000.

All the patients in Group P tolerated the drug well and none of them experienced significant somnolence. So due to all these reasons, it can be used safely in day case young patients.

## CONCLUSION

We conclude that preoperative use of 150 mg of pregabalin two hours before anesthesia has no significant preventive effect on the incidence of succinylcholine induced fasciculations but it may decrease severe fasciculations. However, it can significantly decrease the incidence and severity of succinylcholine-induced myalgia. So its prophylactic use can be recommended in all

## surgical patients requiring short intubation with succinylcholine.

**Conflict of interests:** None declared by the authors. The study was completed by using institutional resources.

### Author contribution:

MAK: Concept, conduct of study, research, manuscript writing, editing

KJS: Concept, manuscript editing

KMA: Statistical analysis

AH: Conduction of Study

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## pregabalin for succinylcholine induced fasciculation and myalgia

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