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SCIENTIFIC ARTICLE

Prophylactic use of pregabalin for prevention of succinylcholine-induced fasciculation and myalgia: a randomized, double-blinded, placebo-controlled study



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KEYWORDS

Pregabalin;
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Abstract

Background: Succinylcholine is commonly used to achieve profound neuromuscular blockade of rapid onset and short duration.

Objective: The present study compared the efficacy of pregabalin for prevention of succinylcholine-induced fasciculation and myalgia.

Design: Prospective, randomized, placebo controlled, double blinded study.

Materials and methods: Patients of both genders undergoing elective spine surgery were randomly assigned to two groups. Patients in Group P (pregabalin group) received 150mg of pregabalin orally 1 h prior to induction of anesthesia with sips of water and patients in Group C (control group) received placebo. Anesthesia was induced with fentanyl 1.5 mcg/kg, propofol 1.5–2.0 mg/kg followed by succinylcholine 1.5 mg/kg. The intensity of fasciculations was assessed by an observer blinded to the group allotment of the patient on a 4-point scale. A blinded observer recorded postoperative myalgia grade after 24 h of surgery. Patients were provided patient-controlled analgesia with fentanyl for postoperative pain relief.

Results: Demographic data of both groups were comparable ($p > 0.05$). The incidence of muscle fasciculation's was not significant between two groups ($p = 0.707$), while more patients in group C had moderate to severe fasciculation's compared to group P ($p = 0.028$). The incidence and severity of myalgia were significantly lower in group P ($p < 0.05$).

Conclusion: Pregabalin 150 mg prevents succinylcholine-induced fasciculations and myalgia and also decreases the fentanyl consumption in elective sine surgery.

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PALAVRAS-CHAVE

Pregabalina;
Succinilcolina;
Fasciculação;
Mialgia

Uso profilático de pregabalina para prevenção de mialgia e fasciculação induzidas por succinilcolina: estudo randômico, duplo-cego e controlado por placebo

Resumo

Justificativa: A succinilcolina é comumente usada para atingir um bloqueio neuromuscular profundo, de início rápido e de curta duração.

Objetivo: O presente estudo comparou a eficácia de pregabalina na prevenção de mialgia e fasciculação induzidas por succinilcolina.

Desenho: Estudo prospectivo, randômico, duplo-cego e controlado por placebo.

Materiais e métodos: Pacientes de ambos os sexos submetidos à cirurgia eletiva de coluna foram aleatoriamente divididos em dois grupos. Os pacientes do Grupo P (pregabalina) receberam 150 mg de pregabalina oral 1 hora antes da indução da anestesia e os pacientes do Grupo C (controle) receberam placebo. A anestesia foi induzida com fentanil (1,5 mcg/kg) e propofol (1,5-2,0 mg/kg), seguidos de succinilcolina 1,5 mg/kg. A intensidade da fasciculação foi avaliada por um observador, cego para a alocação dos grupos, usando uma escala de 4 pontos. Um observador cego registrou o grau pós-operatório de mialgia após 24 horas de cirurgia. Para o alívio da dor no pós-operatório, fentanil foi usado em sistema de analgesia controlada pelo paciente.

Resultados: Os dados demográficos de ambos os grupos eram comparáveis ($p > 0,05$). A incidência de fasciculação muscular não foi significativa entre os dois grupos ($p = 0,707$), enquanto mais pacientes do Grupo C apresentaram fasciculação de moderada a grave em relação ao Grupo P ($p = 0,028$). A incidência e a gravidade de mialgia foram significativamente menores no grupo P ($p < 0,05$).

Conclusão: Pregabalina (150 mg) previne mialgia e fasciculação induzidas por succinilcolina, além de diminuir o consumo de fentanil em cirurgia eletiva de coluna.

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Introduction

Succinylcholine is a short acting depolarizing muscle relaxant with rapid onset and short duration of action. Its use is associated with a number of side effects like fasciculation, postoperative myalgia, increased serum levels of creatine kinase and potassium, malignant hyperthermia, myoglobinuria, raised intraocular pressure and intracranial pressure precluding its routine use.^{1,2} Fasciculations are relatively benign side effects of its use; most anesthesiologists prefer to prevent them due to a possible association between fasciculations and postoperative myalgia.

Different pre-treatment modalities have been attempted to reduce the incidence and severity of fasciculations and myalgia. This includes precurarization with a small dose of non-depolarizing muscle relaxant,³ pre succinylcholine use of lidocaine,⁴ calcium gluconate,⁵ magnesium sulphate,⁶ nonsteroidal anti-inflammatory drugs (NSAIDs),⁷ dexmedetomidine,⁸ benzodiazepines,⁴ remifentanyl,⁹ phenytoin¹⁰ or ketorolac.¹¹ The efficacy of each is variable.

Pregabalin and its predecessor, gabapentin, are analogs of the inhibitory neurotransmitter gammaaminobutyric acid (GABA). As gabapentin¹² has been found to prevent succinylcholine induced fasciculation and myalgia, pregabalin may be an alternative of this with better results.

With this aim, this randomized, double-blinded, placebo-controlled study was instituted to investigate whether use of preoperative pregabalin administration has any effects on succinylcholine-induced fasciculation's and myalgia in

subjects undergoing microdiscectomy under general anesthesia.

Materials and methods

This prospective, randomized, placebo-controlled study was conducted after approval from the Institutional Ethics Committee and written informed consent from the patients undergoing elective spine surgery under general anesthesia. The study was registered at Clinical Trials.gov (Ref.: CTRI/2013/08/003925).

Sixty-four patients, aged 20–60 years, either sex, ASA physical status I or II, scheduled for elective spine surgery were included in the study. Patients with a history of seizure disorders, preoperative ingestion of pregabalin or gabapentin, hyperkalemia, systemic illness like hypertension, diabetes, impaired kidney or liver functions, increased intracranial and intraocular pressure, pregnant or breastfeeding females and patients with known sensitivity to pregabalin were excluded from the study. The patients were randomly allocated to two equal groups with the help of a computer generated table of random numbers to receive following drugs.

Group P (pregabalin group)

Patients received pregabalin 150 mg orally with sips of water, 1 h before the induction of anesthesia.

Table 1 Demographic data.

	Group C (n = 32)	Group P (n = 32)	p-Value
Mean age (yrs)	47.03 ± 10.12	48.87 ± 7.97	0.4212
Male/female	21/11	19/13	0.796
Weight (kg)	61.19 ± 8.30	63.28 ± 10.06	0.367
Spine surgery			
Cervical/thoracic/lumbar	12/1/19	10/0/22	0.496
Duration of surgery (min)	138.69 ± 33.43	133.44 ± 39.42	0.5676

Data are presented as either mean values ± SD or by absolute numbers.

Group C (control group)

Patients received similar looking placebo tablet orally with sips of water, 1 h before the induction of anesthesia.

All the patients were premedicated with oral lorazepam 2 mg and ranitidine 150 mg night before, and 2 h prior to surgery. The study drugs were given to the nurse attendant in identical envelopes marked P and C. The nature of the medications was not known to the nurse attendant who administered the drugs as per instructions.

In the operating room, after establishing the basic monitoring anesthesia was induced by injection (inj.) fentanyl 1.5 mcg/kg, propofol 1.5–2.0 mg/kg and succinylcholine 1.5 mg/kg body weight. The intensity of fasciculation's was assessed by an observer blinded to the group allotment of the patient on a 4-point scale as Absent (0); Mild – fine fasciculation's at the eyes, neck, face or fingers without limb movement (1); Moderate – fasciculation's occurring bilaterally or obvious limb movement (2); Severe – widespread, sustained fasciculation's (3).

The patients were intubated with an appropriate sized cuffed endotracheal tube after assessing complete muscular relaxation by single twitch neuromuscular monitoring. Anesthesia was maintained with oxygen:nitrous oxide (O₂:N₂O; 33:66) and sevoflurane. Vecuronium bromide 0.1 mg/kg was given after endotracheal intubation. Intermittent doses of fentanyl and vecuronium bromide were administered during surgery as indicated. After completion of surgery, neuromuscular blockade was reversed and patients shifted to post anesthesia care unit (PACU).

In PACU patients received postoperative analgesia with fentanyl (5 mcg/mL) through patient controlled analgesia (PCA) pump (Smith Medical ASD, Inc., USA). The total fentanyl requirement in the first 24 h was recorded. Any complications like postoperative nausea, vomiting, dizziness, somnolence, vertigo, confusion, blurred vision and dry mouth were also being recorded and managed accordingly.

The incidence and severity of myalgia were assessed by a blinded observer 24 h after surgical intervention, utilizing a four-point rating scale and graded as: absence of muscle pain (0); muscle stiffness, limited to one area only (1); muscle pain or stiffness noticed spontaneously by the patient, which may require analgesic therapy (2); and generalized, severe or incapacitating discomfort (3).

The postoperative sedation level was assessed by the Ramsay sedation score which consists of the following six grades: anxious (1), cooperative and tranquil (2), responding to commands only (3), brisk response to light glabellar

tap (4), sluggish response to light glabellar tap (5), and no response to light glabellar tap (6).

Sample size calculation was based on the pilot study, where the incidence of fasciculation was found to be 96%. We aimed to decrease the incidence by 50% with pregabalin pre-treatment. With a power of 80% and type I error of 5%, we calculated that 30 subjects were required per group. To take care of any dropouts, we enrolled 32 patients in each group.

Statistical analysis was performed using the Graph pad prism 6.0 statistical software. The demographic data were analyzed by Student *t*-test. Male and female data were analyzed with the Chi square test. The consumption of fentanyl and sedation in groups were analyzed by using Student *t*-test. The incidence and severity of fasciculation and myalgia were analyzed using Fisher's exact test. A *p*-value of <0.05 was considered statistically significant.

Results

Seventy-two patients were assessed for eligibility between September 2013 and February 2014. Sixty-four patients were included in the study after randomization and 61 patients (95.3%) completed the study (Fig. 1). Eight patients were not included in this study on account of patient's refusal (2 patients), preoperative history of analgesic consumption (6 patients). Three patients were excluded from the study following initial randomization on account of need of postoperative ventilator support (2 patients) and PCA pump failure (1 patient); their data has been included in the comparison of demographic profile, however, they were not subjected to further statistical analysis (Fig. 1).

There were no significant differences between the two groups with respect to age, gender, body weight, type and duration of surgery (*p* > 0.05) (Table 1).

The overall incidence of muscle fasciculation's was 83.9% in group P and 90% in group C (*p* = 0.707) (Table 2). The grades of muscle fasciculation's observed were mild (57.7%), moderate (34.6%) and severe (7.7%) in Group P, while 22.2%, 59.2%, and 18.5% respectively in Group C. More patients in Group C had moderate to severe fasciculation's compared to Group P (*p* = 0.028).

Six (19.3%) patients of group P and 14 (46.7%) patients of group C had postoperative myalgia after 24 h (*p* = 0.03) (Table 3). The severity of myalgia was less in the group P compared to group C (5 and 1 vs. 10 and 4 of Grade 1 and 2 myalgia respectively). None of the patients complained

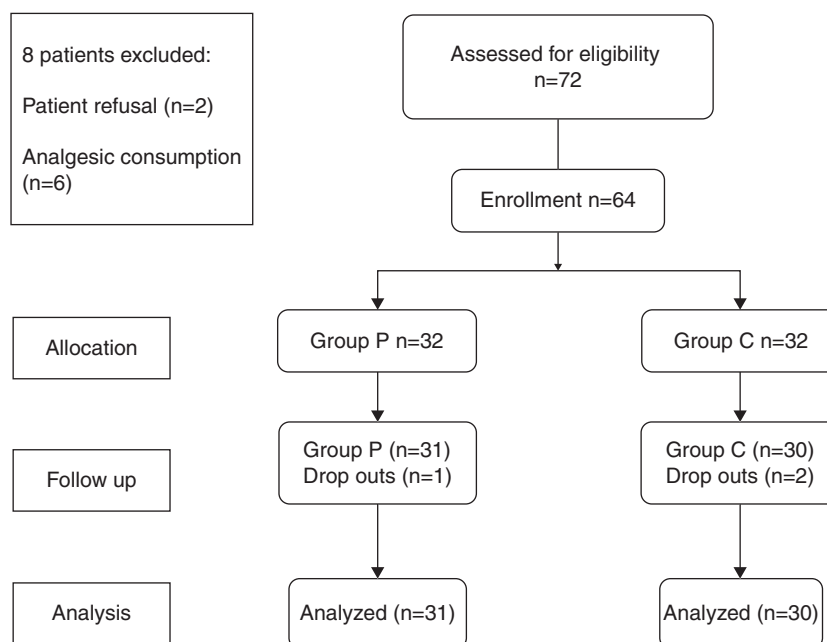


Figure 1 Study design.

Table 2 The incidence and severity of fasciculations.

	Group C (n = 30)	Group P (n = 31)	p-Value
<i>Fasciculations</i>			
No	3 (10%)	5 (16.1%)	0.707
Yes	27 (90%)	26 (83.9%)	
<i>Severity of fasciculations</i>			
Mild	6 (22.2%)	15 (57.7%)	0.028
Moderate	16 (59.2%)	9 (34.6%)	
Severe	5 (18.5%)	2 (7.7%)	

Data are presented as numbers with percentage.

of myalgia of grade 3 in any study groups. No association between the incidence/grade of fasciculation's and myalgia was demonstrated.

The consumption of fentanyl in the first 24h was significantly less in the group P compared to the group C (674.03 ± 137.84 mcg vs. 1002.67 ± 214.43 mcg) ($p < 0.001$). Sedation score was significantly higher in group P ($p = 0.004$) (Table 4).

Table 3 The incidence and severity of myalgia.

	Group C (n = 30)	Group P (n = 31)	p-Value
<i>Myalgia</i>			
No	16 (53.3%)	25 (80.7%)	0.030
Yes	14 (46.7%)	6 (19.3%)	
<i>Severity of myalgia</i>			
Mild	10 (71.4%)	5 (83.3%)	0.020
Moderate	4 (28.6%)	1 (16.7%)	
Severe	0	0	

Data are presented as numbers with percentage.

Discussion

Succinylcholine is the best drug for rapidly providing ideal conditions for short procedures requiring endotracheal intubation. Unfortunately, its use is associated with muscular fasciculation's and postoperative myalgia.

Fasciculation produced by succinylcholine have been attributed to a prejunctional depolarizing action of succinylcholine, resulting in repetitive firing of the motor nerve terminals and antidromic discharges that manifests as an uncoordinated muscle contractions.¹³ Various drugs have been found to influence the fasciculation's and the mechanisms proposed ranges from impairing release of acetylcholine by morphine and narolphine,⁹ impair neurohumoral transmission at peripheral muscarinic receptors by morphine,⁹ blocking the prejunctional receptors by non depolarizing muscle relaxants,³ motor nerve membrane stabilization by reduction of calcium ions by diphenylhydantoin,¹⁰ inhibition of calcium release leading to decrease in acetylcholine release by magnesium.⁶

The mechanism of the inhibitory action of pregabalin on succinylcholine induced muscle fasciculation is unclear. Since intracellular calcium accumulation is important for enhancing the speed and strength of the fasciculation's and the contraction of the intrafusal muscle fibers, the effect of pregabalin on voltage-gated calcium channels may be a possible mechanism of decreasing the muscle contractions leading to fasciculation's.¹⁴

Postoperative myalgia following the use of succinylcholine is a common, troublesome clinical problem. Succinylcholine-induced postoperative myalgia is most frequent on the first postoperative day. The exact pathophysiology for succinylcholine induced myalgia is not clear. Various proposed mechanisms of its causation include increased myoplasmic calcium concentrations, membrane phospholipids degradation, released free fatty acids, and

Table 4 Postoperative sedation score (Ramsay sedation score) and fentanyl consumption within 24 h after surgery.

	Group C (n = 30)	Group P (n = 31)	p-Value
Fentanyl requirements (mcg)	1002.67 ± 214.43	674.03 ± 137.84	<0.0001
Sedation score	2.27 ± 0.66	2.71 ± 0.69	0.0048

Data are presented as mean values ± SD.

free radicals responsible for muscle damage leading to postoperative myalgia.¹⁵⁻¹⁸ Various drugs have been utilized to look into blocking these specific targets to decrease myalgia.

Pregabalin inhibits Ca²⁺ currents via high-voltage-activated channels containing the $\alpha_2\delta$ subunit,¹⁹ reducing neurotransmitter release (e.g. glutamate, substance P, calcitonin, noradrenaline, gene-related peptide) and attenuating the postsynaptic excitability,¹⁴ providing the basis for its antinociceptive efficacy in post-operative pain.^{20,21} The above facts may also be a plausible explanation for its efficacy in reducing succinylcholine induced myalgia.

We utilized pregabalin over gabapentin to assess its effect on fasciculation and myalgia as pregabalin has higher bioavailability (90% vs. 33-66%), rapid absorption (with peak plasma levels at: 1 h vs. 3-4 h) and a linear increase in plasma concentration as its dose is increased. Lower doses of pregabalin than that of gabapentin (2-4-fold lower doses) have a similar analgesic effect on neuropathic pain, which makes pregabalin more advantageous in terms of the side effects of dosage.²²

Use of induction agents like thiopentone or propofol have been demonstrated to have no bearing on succinylcholine induced fasciculation though less myalgia is seen when thiopentone is used in comparison to propofol.¹⁵ Maddineni et al.²³ observed that there is no difference in postoperative myalgia when propofol was substituted for thiopentone but according to McClymont,²⁴ propofol is better than thiopentone to control myalgia.

Our study is in agreement with various studies of reduction of postoperative pain as well as opioids requirements with the use of preoperative pregabalin. Reuben and colleagues²⁵ observed that use of preoperative pregabalin in patients undergoing lumbar laminectomy was as effective as celecoxib in reducing postoperative pain and patient-controlled morphine consumption. Agarwal et al. reported effectiveness of the single preoperative oral dose of 150 mg pregabalin in reducing postoperative pain and fentanyl consumption in laparoscopic cholecystectomy.²⁶

There are some limitations with this study: (a) the study design was observational, and we measure a subjective variable (fasciculation) rather than objective variables (increase in potassium, myoglobin, and CPK) and (b) this is a single institutional study and our results may not be generalized. Further studies in different settings and group of patients may give a better understanding of use of pregabalin.

Conclusion

Our study demonstrated that the preoperative administration of 150 mg pregabalin significantly decreased the severity of muscle fasciculation's, without an effect on its incidence. It also decreased the incidence and severity of

succinylcholine-induced myalgia as well as postoperative fentanyl consumption.

Conflicts of interest

The authors declare no conflicts of interest.

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