

A Randomized Controlled Trial to Compare Preemptive Analgesic Efficacy and Safety of Pregabalin and Gabapentin for Succinylcholine-Induced Myalgia

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Abstract

Background: Succinylcholine is a drug of choice for rapid induction of anesthesia but produces postoperative myalgia. Preemptive analgesia is intended to decrease perception of pain before exposure to painful stimuli. Pregabalin and gabapentin, analogs of the inhibitory neurotransmitter gamma aminobutyric acid, are effective in several models of neuropathic pain, incisional, inflammatory, and formalin-induced injury. However, the data available on their preemptive analgesic efficacy in succinylcholine myalgia are sparse. This study was designed to compare the preemptive analgesic efficacy and safety of pregabalin and gabapentin. **Materials and Methods:** This randomized clinical trial included 120 surgical patients of either sex, between 18 and 70 years, and of American Society of Anesthesiologists-I/II grade. Patients were randomly allocated to control and test groups; received respective treatments 30 min before induction of anesthesia. Myalgia and pain scores were recorded using the myalgia scale and visual analog/ facial rating scale at awakening at 6, 12, 18, and 24 h, respectively. Postoperative analgesic requirement over 24 h was recorded. Data were analyzed using OpenEpi (Andrew G. Dean and Kevin M. Sullivan, Atlanta, GA, USA) statistical softwares. **Results:** Significantly lower pain scores were observed in the pregabalin group at 6, 12, and 24 h, and in gabapentin group at 24 h as compared to control and placebo ($P < 0.05$). They were however found to be equianalgesic when compared to each other ($P > 0.05$). Pregabalin-treated patients were more comfortable throughout with significantly less postoperative myalgia and analgesic requirement ($P < 0.05$). **Conclusions:** Results strongly suggest the preemptive analgesic efficacy of a single oral dose of pregabalin and gabapentin over diclofenac in postoperative myalgia and pain management. However, on the basis of safety profile, pregabalin may be preferred over gabapentin in succinylcholine-induced myalgia.

Keywords: Aldrete's scale, facial rating scale, preemptive analgesia, pregabalin, succinylcholine myalgia, visual analog scale

INTRODUCTION

Succinylcholine has fast onset and short duration of action and hence is considered as drug of choice for rapid sequence induction of anaesthesia.¹ Intubation becomes easier owing to intense neuromuscular blockade produced by succinylcholine.² However, it produces muscle stiffness and postoperative myalgia as side effects.^{3,4} The incidence of succinylcholine-induced myalgia ranges from 41% to 92%.⁵ Succinylcholine-induced myalgia is prominent in the muscles of the shoulder, neck, back, and abdomen. It is predominantly seen in surgeries that permit early ambulation. The exact underlying mechanism of succinylcholine-induced myalgia is not known, but several mechanisms including increased myoplasmic calcium concentrations, degradation of membrane phospholipids, release of free fatty acids, and free radicals are

thought to be causative factors.⁶ Use of different pretreatment modalities including benzodiazepines, nondepolarizing neuromuscular blockers, local anesthetics, chlorpromazine, phenytoin, ketorolac, Vitamin E derivatives, pretreatment with rocuronium and remifentanyl have been tried to reduce the severity of succinylcholine-induced myalgia.⁷⁻¹⁴

The surgical procedure serves as noxious stimulus, results in initial sensitization and establishment of altered processing of afferent input to central nervous system (CNS), following

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an incisional and inflammatory injury which amplifies postoperative pain. Preemptive analgesia is a treatment that is initiated before the surgical procedure to “preempt” or prevent neurophysiological and biochemical consequences of a noxious input to the CNS provoked by the procedure. It means that the concept of preemptive analgesia is not to prevent pain but to prevent CNS alterations leading to pain amplification following first pain experience and development of chronic pain syndromes.¹⁵ Preemptive analgesic efficacy of drugs such as opioids, local anesthetics, and nonsteroidal anti-inflammatory drugs have been demonstrated in earlier studies.¹⁶⁻¹⁸

The use of gabapentin and pregabalin, as protective premedication before the start of different surgeries, has been demonstrated in separate studies.¹⁹ To the best of our knowledge, no comprehensive data exist with regard to comparison of preemptive analgesic efficacy and safety of pregabalin and gabapentin for succinylcholine-induced myalgia. The present randomized controlled trial was therefore designed to investigate the preemptive analgesic efficacy and safety of pregabalin and gabapentin for succinylcholine-induced myalgia.

Pregabalin and gabapentin are newer antiepileptic drugs. This class of drugs works through three major mechanisms, i.e., potentiation of gamma aminobutyric acid transmission, reduction of glutamate-mediated excitatory transmission, and blockade of voltage-activated ion channels. The latter mechanism of action, in particular, is responsible for the success of these agents as preemptive analgesic.¹⁵

Gabapentin binds to the $\alpha 2$ - δ subunit of voltage-dependent calcium channels and reduces calcium influx into nerve terminals, which inhibits release of endogenous excitatory amino acids aspartate and glutamate thereby reduces postsynaptic excitability.^{20,21} While pregabalin is an analog of gabapentin and has a similar mechanism of action as gabapentin. It reduces pain by decreasing calcium influx into the intrafusal muscle fibers.²²

MATERIALS AND METHODS

The Institute’s Ethics Committee approved this study protocol, and written informed consent was obtained from each participant (Ref. SKNMC/Ethics/APP/2018/380). The study duration was 12 months. The sample size calculation was done using open-Epi statistical software (power - 80%, confidence interval - 95%, odds ratio - 6); the study had 4 groups with 30 patients in each group for a power of 80% ($\beta = 80\%$ and $\alpha = 0.05$). Patients, between 18 and 70 years of age of either gender, American Society of Anesthesiologists I and II, undergoing surgeries under general anesthesia requiring endotracheal intubation, from departments of surgery and ear, nose, and throat were recruited. Patients with known or suspected coagulopathy, hypersensitivity to any of the study drugs, mental retardation/preexisting neurological disease, impaired renal functions, history of analgesic consumption,

history of peptic ulcer disease, or treatment with antacids were excluded.

All patients were assessed preoperatively the day before surgery. Study protocol was explained to participants. Participants were randomly assigned to one of the four groups using a computer-generated table of random numbers, to receive medications.

- Group A (Pregabalin group): Pregabalin 150 mg 30 min before surgery
- Group B (Gabapentin group): Gabapentin 600 mg 30 min before surgery
- Group C (Control group): Diclofenac sodium 100 mg 30 min before surgery
- Group D (Placebo group): Saccharine tablet 10 mg 30 min before surgery.

In the operating room, standard monitoring was used. An 18G intravenous cannula was inserted in the dorsum of the nondominant hand. Premedication was with injection glycopyrrolate 0.02 mg/kg + injection midazolam 0.02 mg/kg i.v. preoxygenation was done with 100% oxygen for 3 min before induction. Anesthesia was induced with propofol 1.5–2 mg/kg and fentanyl 3 μ g/kg, and intubation, with appropriate-sized and cuffed endotracheal tube, was facilitated by injection succinylcholine 1.5 mg/kg. Anesthesia was maintained with 50% nitrous oxide in oxygen and sevoflurane. Vecuronium bromide 100 μ g/kg was given after endotracheal intubation. Fentanyl 1 μ g/kg/h was infused during surgery, and vecuronium bromide 20 μ g/kg was given intermittently to maintain muscle relaxation. At the completion of surgery, residual neuromuscular blockade was reversed with glycopyrrolate 10 μ g/kg and neostigmine 40 μ g/kg intravenously, and patients were extubated when adequate spontaneous ventilation was established. Patients were transferred to the postanesthesia care unit from where they were transferred to their respective wards. Baseline and postoperative vital parameters such as pulse rate, respiratory rate, mean arterial pressure, and saturation of peripheral oxygen (SpO₂) were recorded.

Myalgia was defined as “muscle pain not related to surgical intervention.”²³ The incidence and severity of myalgia were recorded by a blinded observer after surgical intervention for the first 24 h.

The grading of myalgia was done as follows:⁶

- 0 - Absence of muscle pain
- 1 - Stiffness limited to one area only
- 2 - Muscle pain or stiffness noticed spontaneously by the patient, which may require analgesic therapy
- 3 - Generalized, severe, or incapacitating discomfort.

Postoperative level of analgesia was noted on visual analog scale (VAS) and facial rating scale (FRS) at 6, 12, 18, and 24 h. Rescue analgesic (Diclofenac 100 mg) was given if patient complained of pain or pain score was more than 4.²⁴ Postoperative analgesic requirement for 24 h was recorded.

Duration of postoperative anesthesia care unit stay was recorded using modified Aldrete’s scoring system; patients with score >9 were shifted to the ward.²⁴

Study design

See Figure 1.

Statistical analysis

Demographic profile and vital parameters were analyzed using analysis of variance. VAS and FRS were analyzed using Student’s *t*-test. Analgesic consumption was compared using Mann–Whitney U-test.

RESULTS

In this randomized clinical study, preemptive analgesic efficacy of pregabalin (150 mg), gabapentin (600 mg), and diclofenac (100 mg) single dose taken orally in postoperative pain and succinylcholine-induced myalgia was compared. There were 83 males and 37 females enrolled in the study. Demographic profile and vital parameters were comparable among groups presented in Tables 1 and 2.

Effect of test drugs on pain scores and myalgia scale are presented in Tables 3 and 4, respectively. Pain scores on both scales were found significantly lower at 6, 12, and 24 h in the pregabalin group when compared to control as well as placebo groups, whereas in the gabapentin group, it was found significantly lower only at 24 h when compared to control. However, pregabalin and gabapentin were both found equianalgesic in this regard since no significant difference was found when compared to each other.

Incidence and severity of myalgia were minimal in the pregabalin group with significantly less requirement of rescue analgesic [Table 5]. Nausea, vomiting, and sedation were observed as side effects among the groups which were of mild variety. Patients in the pregabalin group were found to be more comfortable throughout in this regard as adverse drug reactions, i.e., nausea, vomiting, and sedation were less in pregabalin group compared to gabapentin, control, and placebo groups.

DISCUSSION

Succinylcholine is a depolarizing neuromuscular-blocking agent. It is considered as the best drug for rapid sequence induction and also for providing suitable muscle relaxation for surgical procedures of short duration. However, the use of succinylcholine is frequently accompanied by postoperative myalgia.^{4,25} The reported incidence of succinylcholine-induced myalgia varies between 41% and 92%.⁵ Succinylcholine-induced myalgia is usually experienced from the first day after surgery and usually lasts for about 3–4 days. While this myalgia is self-limiting, iatrogenic postoperative myalgia is considered unacceptable in modern anesthetic practice.²⁶ Postoperative myalgia is influenced by gender, females being affected more often.²⁷ It is also observed more commonly in patients who take to early ambulation.⁷ In our study, myalgia was observed in 46 female and 30 male patients; this is in agreement with the study observations that mention myalgia is influenced by gender.

Postoperative myalgia is likely a consequence of muscle damage produced by the shearing forces associated with the

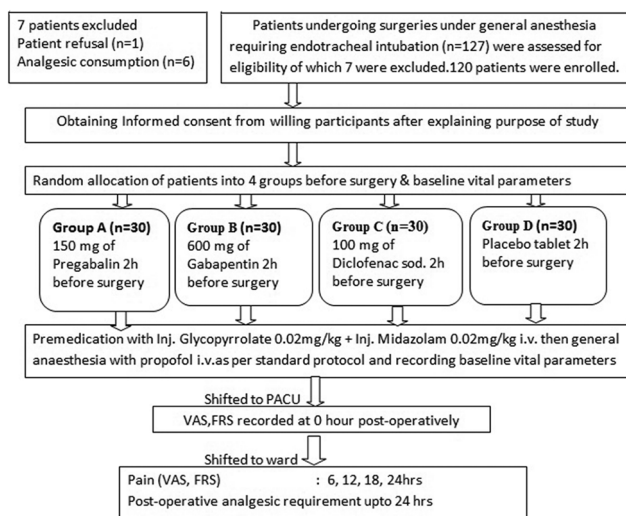


Figure 1: Study flow chart

Table 1: Demographic profile of patients

Characteristics (n=120)	Group A (pregabalin)	Group B (gabapentin)	Group C (control)	Group D (placebo)
Age (years), mean±SD	46.6±9.67	44.36±8.84	46.96±8.75	46.13±9.83
Sex (male:female)	21:9	22:8	17:13	23:7
Weight, mean±SD	71.6±9.95	74.5±11.59	71.23±10.94	68.76±8.15
Surgery performed				
Tonsillectomy	3	5	4	6
Laparoscopic cholecystectomy	6	7	8	8
Tympanoplasty	9	8	8	8
Hemithyroidectomy	1	3	2	0
Near-total thyroidectomy	2	0	1	2
Mastoid exploration	9	7	7	5
Duration of surgery (min)	120±15.53	122.66±15.29	127±15.78	126±14.99

Baseline vital parameters were comparable between the groups. SD – Standard deviation

fasciculations at the onset of phase one block.²⁸ At molecular level, occurrence of postoperative myalgia is due to increased myoplasmic calcium concentrations, membrane phospholipids' degradation, released free fatty acids and free radicals which cause damage to delicate muscle spindles.^{6,29} Pain signals from damaged tissue launch a series of changes in the somatosensory system. One of them is an increase in the responsiveness of both peripheral and central neurons. These changes will increase the response to subsequent stimuli thereby amplifying pain.³⁰

Preemptive analgesia is a treatment that is intended to reduce the physiological consequences of nociceptive transmission provoked by the procedure. It is administered before the surgical procedure. Due to this "protective" effect on the pain pathways, preemptive analgesia has the potential to be more effective than a similar analgesic treatment initiated after surgery. Consequently, it helps to reduce immediate postoperative pain and to prevent development of chronic pain.³¹

Table 2: Effect on postoperative vital parameters

Drugs group (mean±SD)	Baseline	At 0 h postoperatively
Group A		
Pulse rate	79.1±8.2	79.1±8.2
Respiratory rate	13.3±1.2	13.3±1.2
SpO ₂	99.9±0.25	99.8±0.4
MAP	78.4±6.2	78.5±6.0
Group B		
Pulse rate	81.8±8.9	81.8±8.9
Respiratory rate	13.6±1.6	13.6±1.6
SpO ₂	99.9±0.3	99.9±0.2
MAP	80.1±5.1	80.4±5.5
Group C		
Pulse rate	81.9±8.6	81.9±8.6
Respiratory rate	13.6±1.7	13.6±1.7
SpO ₂	99.9±0.3	99.9±0.3
MAP	80.7±5.5	80.7±5.5
Group D		
Pulse rate	84.0±7.5	84.6±7.5
Respiratory rate	13.5±1.8	13.4±1.8
SpO ₂	99.8±0.4	99.9±0.2
MAP	80.9±6.2	81.9±5.1

MAP – Mean arterial pressure, SD – Standard deviation, SpO₂ – Saturation of peripheral oxygen

In the present study, we have studied and compared preemptive analgesic efficacy and safety of diclofenac sodium, and two antiepileptic drugs such as gabapentin and pregabalin. In our previous study, we found gabapentin to have better preemptive analgesic efficacy in postoperative pain management compared to diclofenac sodium;¹⁵ however, this efficacy in postoperative succinylcholine-induced myalgia was not studied. NSAIDs-mediated relief of myalgia is suggestive of an inflammatory genesis and involvement of prostaglandins,^{9,29} indicative of their peripheral action mainly. It is also postulated that calcium influx will eventually lead to muscle damage and pain through contraction of the intrafusal muscle fibers.^{32,33} Gabapentin is known to bind to the α2-δ subunit of voltage-dependent calcium channels.²⁰ It reduces calcium influx into nerve terminals and inhibits release of endogenous excitatory amino acids aspartate and glutamate thereby reduces postsynaptic excitability²¹ suggestive of more specific action on muscle fires through voltage-dependent calcium channels. Hence, gabapentin is thought to be more useful in preventing postoperative pain and myalgia compared to NSAIDs. Our study results revealed the same as: pain scores and frequency of myalgia were found to be significantly lower in gabapentin group when compared to diclofenac group.

Table 3: Effect on postoperative visual analog scale, facial rating scale, and adverse drug reactions

Drugs group	Time (h), mean±SD					ADRs
	0	6	12	18	24	
Group A (pregabalin)						
VAS	1.5±0.7	2.9±1.1*#	3.0±1.3*#	2.7±1.1#	1.4±1.5*#	Nausea - 0
FRS	2.3±1.5	1.5±0.7*#	3.2±1.1*#	3.9±1.4	1.9±1.1*#	Vomiting - 6 Sedation - 2
Group B (gabapentin)						
VAS	1.4±0.8	3.4±1.2	3.3±1.2#	2.8±0.9#	1.7±1.9*#	Nausea - 1
FRS	2.7±1.9	2.4±0.8#	3.5±1.2	3.4±1.2#	2.1±0.9*#	Vomiting - 11 Sedation - 8
Group C (control)						
VAS	1.4±1.0	3.9±1.5	3.9±1.8	2.9±0.7#	2.6±1.7#	Nausea - 2
FRS	2.6±1.7	2.4±1#	3.9±1.5	3.7±1.9	2.9±0.7#	Vomiting - 13 Sedation - 2
Group D (placebo)						
VAS	1.4±1.0	4±1.5	4±1.9	3.8±1.3	3.8±1.6	Nausea - 4
FRS	2.8±1.6	3.4±1.0	4±1.5	4±1.9	3.9±1.3	Vomiting - 18 Sedation - 0

n=120, #P<0.05 compared to placebo, *P<0.05 compared to control. VAS – Visual analog scale, FRS – Facial rating scale, ADRs – Adverse drug reactions, SD – Standard deviation

Table 4: Grades of succinylcholine-induced myalgia

	Group A (pregabalin)	Group B (gabapentin)	Group C (control)	Group D (placebo)
Myalgia				
Yes - male (female)	6 (7)	7 (8)	8 (15)	9 (16)
No	17	15	7	5
Frequency of myalgia (%)	43.34	50	76.67	83.34%
Severity of myalgia				
Mild	12	9	16	16
Moderate	1	6	7	8
Severe	0	0	0	1

Table 5: Postoperative rescue analgesic requirement

Drug group	Analgesic needed in 24 h (g)	Per patient requirement median (IQR)
Group A	800	0 (0-100)*.#
Group B	1900	50 (0-100)#
Group C	2400	50 (0-100)#
Group D	3100	100 (100-100)

	Time of rescue analgesic administration		
	0-6 h	6-12 h	12-24 h
Group A	0	400	400
Group B	0	700	1200
Group C	0	1000	1400
Group D	0	1400	1700

* $P < 0.05$ compared to control (Group C), # $P < 0.05$ compared to placebo (Group D), by Mann-Whitney U-test for per patient analgesic requirement. IQR – Interquartile range

Pregabalin being an analog of gabapentin has a similar mechanism of action and reduces pain by decreasing calcium influx into the intrafusal muscle fibers. However, pregabalin has a better bioavailability (90%), is rapidly absorbed, and has better pharmacokinetic profile than gabapentin. It requires a lower dose and is associated with fewer dose-related adverse effects, while still maintaining an equianalgesic effect.²² Some earlier studies have demonstrated the equianalgesic efficacy of pregabalin (150 mg), gabapentin (600 mg), and diclofenac sodium (100 mg) in reducing the incidence and severity of succinylcholine-induced myalgia.^{22,34} In our study, pregabalin (150 mg) has better efficacy than diclofenac (100 mg) as VAS scores show significant difference at 6, 12, and 24 h. Better efficacy of pregabalin is due to its multifaceted action for pain control including that of neuropathic origin, while diclofenac is involved in suppression of pain from only inflammatory origin. Gabapentin shows significant difference in VAS at 24 h when compared to diclofenac. This also indicates faster onset and sustained action of pregabalin compared to gabapentin, thereby reducing the consumption of postoperative rescue analgesic. The incidence of adverse drug effects is also less in the pregabalin group as compared to gabapentin and diclofenac.

Although pregabalin and gabapentin have equal analgesic efficacy, pregabalin (150 mg) has faster onset and sustained action requiring less postoperative rescue analgesic and better

safety when compared to gabapentin (600 mg). Hence, on the basis of safety and efficacy parameters, single preemptive oral dose of pregabalin (150 mg) can be recommended as preemptive analgesic in postoperative pain management and in reducing the incidence and severity of succinylcholine-induced myalgia.

CONCLUSIONS

Our clinical study has demonstrated pregabalin (150 mg) as a better choice when compared to gabapentin (600 mg) and diclofenac (100 mg) in reducing the incidence and severity of succinylcholine-induced myalgia and postoperative pain. Preemptive pregabalin has a faster onset, sustained actions, reduced postoperative analgesic requirement, and better safety profile than gabapentin and diclofenac. It may therefore be preferred over gabapentin and diclofenac.

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Conflicts of interest

There are no conflicts of interest.

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