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Effect of Pregabalin on Succinylcholine Induced Fasciculation, Myalgia and Hyperkalemia in Spine Surgery

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Abstract

A randomized control trial was done between January and December of 2018, in the Department of Anaesthesia, Analgesia, Palliative & Intensive Care Medicine of Dhaka Medical College Hospital, Bangladesh, to evaluate the preventive effect of pregabalin on succinylcholine induced adverse effects, i.e., fasciculation, myalgia and hyperkaliemia in spine surgery. Sixty patients of elective spine surgery under general anaesthesia were selected and divided into two groups. Pregabalin 150 mg was given to one group and matching placebo was given to another group orally with sips of water one hour before surgery. Succinylcholine 1.5 mg/kg was given after induction agent. Muscle fasciculation was observed just after succinylcholine administration. Serum potassium was measured 5 minutes before induction and 5 minutes after succinylcholine administration. After completion of surgery reversal was given. Time of first analgesic demand was recorded. Injection Morphine 0.15 mg/kg intramuscular was given when patient complained about pain. Myalgia (muscle pain not associated with surgery) was observed 24 hours after anaesthesia and total morphine consumption was recorded. Use of pregabalin 150 mg one hour before surgery reduced the severity of fasciculation and the incidence and severity of postoperative myalgia. It also reduced the rise of serum potassium concentration after succinylcholine administration though the rise was within normal limit. Pregabalin also reduced the total opioid consumption after surgery.

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Introduction

Patients undergoing general anaesthesia usually need endotracheal intubation. Muscle relaxants are used for this purpose and succinylcholine is still the most commonly used agent. Succinylcholine is a depolarizing muscle relaxant, produces profound neuromuscular block with rapid onset but short duration.[1] However, using succinylcholine is associated with a number of adverse effects like fasciculation, postoperative myalgia, increased serum levels of creatine kinase and potassium, malignant hyperthermia, myoglobinuria, and raised intraocular and intracranial pressure.[2]

From above complications fasciculation immediately after administration of succinylcholine and subsequent myalgia in postoperative period outnumber the rest.

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These side effects are very embarrassing for the patients especially for day care patients as because postoperative myalgia may delay their discharge from the hospital.[3] Postoperative myalgia is particularly prominent in the muscles of neck, back, shoulder and abdomen. The exact mechanism of myalgia is not known but stimulation of presynaptic acetylcholine receptors and contraction of intrafusal fibers of muscle spindles may contribute.[1] Postoperative myalgia can last for several days and may be a cause of significant discomfort to patients.[4] Postoperative myalgia may be the causes of increased serum concentration of potassium, myoglobin and creatinine kinase.[5]

Different pre-treatment modalities have been attempted to reduce the incidence and severity of fasciculation and myalgia. This includes precurarization with a small dose of non-depolarizing muscle relaxant, pre succinylcholine use of lidocaine, magnesium sulphate, calcium gluconate, nonsteroidal anti-inflammatory drugs (NSAIDs), dexmedetomidine, benzodiazepines, remifentanil, phenytoin, vitamin C and vitamin E derivatives and gabapentin and all have been tried with variable success.[2,4]

Hyperkalemia following succinylcholine was recognized several years after its clinical introduction.[6] Succinylcholine can cause a transient increase in the plasma potassium concentration. This is thought to be the result of the release of potassium from skeletal muscle during depolarization. In healthy adults this increase does not usually exceed 0.5 mmol/liter and is unlikely to be harmful. Succinylcholine induced lethal hyperkalemic response can result in certain susceptible individuals.[7] However, arrhythmias can occur during anaesthesia in patients with burns, massive trauma, tetanus, spinal cord injury and particularly in renal failure patients.[8] Even cardiac arrest has also been occurred in burned patient after administration of suxamethonium.[9]

An antiepileptic drug, pregabalin was also tried recently in a different clinical study to assess the incidence and severity of fasciculation and myalgia in patients of spine surgeries.[3] Some studies has done to evaluate the effectiveness of pregabalin on succinylecholine induced fasciculation and myalgia but none of them tried to find out succinylecholine induced hyperkalemia. Though there are some studies with rocuronium, magnesium sulphate, precurarization, using different dose of succinylcholine have been used to evaluate their effects on succinylcholine regarding hyperkalaemia. As there is association between fasciculation with myalgia there may be a relation with hyperkalemia also as muscle fiber may damage during the fasciculation produced by suxamethonium. Those are important concerns during surgical procedure done under general anesthesia. Therefore, our study aims to evaluate the effect of pregabalin on succinylcholine-induced adverse effects like fasciculation, myalgia and hyperkalemia in subjects undergoing spine surgery (PLID) under general anesthesia.

Methods

This randomized control trial was carried out in the Department of Anaesthesia, Analgesia, Palliative & Intensive Care Medicine of Dhaka Medical College Hospital, Dhaka, Bangladesh, between January and December of 2018. Sixty patients aged 18-50 years, of either sex having ASA physical status I or II and as scheduled for

elective spine surgery, were included in this study.

Patient who had history of hypersensitivity to the study drug, seizure, hypertension, Pregnant or breast-feeding female and who had received analgesics or sedatives within 24 hours before surgery were excluded from the study. Then the patients were randomly assigned to one of the two groups using a computer-generated table of random numbers and each group contains 30 patients.

All patients received oral midazolam 7.5 mg and ranitidine 150 mg on the night before surgery. Group I patients received 150 mg pregabalin orally with sips of water 1 hour before scheduled surgery and Group II patients received matching placebo orally with sips of water 1 hour before scheduled surgery. After arrival into the operation theatre, intravenous cannulation was done and non-potassium containing intravenous fluid normal saline (0.9% sodium chloride) was given in both groups. Baseline standard monitoring for example Pulse, NIBP, SpO_2 were monitored throughout the operative period. The first blood sample was collected 5 minutes before induction of anaesthesia and sample was sent to the Department of Clinical Pathology, Dhaka Medical College Hospital for measurement serum potassium level. Pre-oxygenation was done with 100% O_2 for 5 minutes to all patients. Anaesthesia was induced with fentanyl 1.5 µg/kg, thiopental sodium 5mg/kg. Loss of eye lash reflex was considered as the endpoint of induction. At this point injection succinylcholine 1.5 mg/kg IV were administered. During this period patients were monitored regarding fasciculation. The degree of muscle fasciculation after administration of succinylcholine was recorded and graded on a four-point scale as follows:

0= No fasciculation.

1= Mild (fine fasciculations at the eyes, neck, face or fingers without limb movement).

2= Moderate (fasciculations occurring bilaterally or obvious limb movement).

3= Severe (when widespread, sustained fasciculation more than one minute).

Endotracheal intubation was performed 1 minute after succinylcholine administration with appropriately sized endotracheal tube. Bilateral breath sound was confirmed for correct positioning of the tube. Anaesthesia was maintained with oxygen 33%, nitrous oxide 66% and halothane 0.6% supplementation. After the effect of succinylecholine was over muscle relaxation was maintained by vecuronium bromide 0.1mg/kg bolus and incremental dose of .03mg/kg whenever needed. Pulse, Blood pressure and SpO_2 were monitored and recorded. 2nd Blood sample was collected to measure serum potassium concentration 5 minutes after administration of succinylcholine and was sent to the Department of Clinical Pathology, Dhaka Medical College Hospital. Infusion of normal saline was used for deficit and maintenance according to body weight.

After completion of operation halothane was switched off. Finally, after fulfilling the reversal criteria patient was reversed with atropine 15 µg/kg and neostigmine 35 µg/kg intravenously and was extubated when patient become awake and then transferred to post-anesthesia care unit (PACU).

In the postoperative room, all patients received with inj. Paracetamol 1gm IV 6 hourly for analgesia. Time of first analgesic (morphine)

demand was then recorded.

Intramuscular injection of morphine 0.15 mg/kg was given when patient complained pain according to VAS score 6 or above. To all patients, ondansetron 8mg IV was given along with 1st dose of Morphine. The presence and severity of pain were assessed using a visual analogue scale (VAS) for pain at rest and continued it at 4 hours interval up to 24 hours and in between 4 hours whenever patient complained about pain. Total morphine requirement was documented. The incidence and severity of myalgia was recorded after 24 hours of surgical intervention utilizing a four-point rating scale and graded as:

0= Absence of muscle pain

1= pain or stiffness limited to one area only

2= Muscle pain or stiffness noticed spontaneously by the patients, which may require analgesic therapy

3= Generalized, severe or incapacitating discomfort

Incidence of nausea and vomiting were also being recorded. Measurement of sedation was done after 24 hours of operation by Ramsay Sedation Score which consists of the following six grades:

1: Anxious and agitated or restless, or both.

2: Co-operative, oriented and tranquil

3: Responds to commands only.

4: Brisk response to light tactile stimuli or loud auditory stimulus.

5: Sluggish response to light tactile stimuli or loud auditory stimulus.

6: No response.

Statistical analyses were done by using Statistical Package for Social Sciences (SPSS) version 22.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Unpaired student t-test was used for continuous variables like age, VAS score, serum potassium level, total morphine consumption, time of first analgesic demand and Ramsay sedation score. Chi-Square test was used to analyze the categorical variables like ASA class, fasciculation, myalgia, occurrence of nausea and vomiting. A P value <0.05 was considered as statistically significant. The study was approved by the Ethical Review Committee of Dhaka Medical College, Dhaka, Bangladesh.

Results

The mean age of the study participants was 41.13±9.63 years and 38.63±9.82 years in group I and group II respectively. The differences between two groups were not statistically significant (Table I). 4(13.3%) patients of group I and 2(6.7%) patients of group II had no fasciculation. According to severity of fasciculation, 18(69.2%) patients of group I and 5(17.9%) patients of group II had mild fasciculation. Moderate fasciculation had been observed in 6(23.1%) patients of group I and 19 (67.9%) patients of group II. In Group I only 2(7.7%) patients had severe fasciculation but in group II 4(14.3%) patients developed severe fasciculation. From this table it was found that fasciculation was reduced in the study group which was statistically significant (P=0.001) between two groups (Table-II). 13(43.3%) patients of group I and 5(16.7%) patients of group II had not developed myalgia. According to severity myalgia 12(70.6%) patients had mild, 4(23.5%) patients had moderate and 1(5.9%) patient had severe myalgia in group I. However, in group II there was 7(28%) patients had mild, 16(64%) patients had moderate and 2(8%)

patients had severe myalgia. From this table it was found that myalgia was decreased in group I which was statistically significant between two groups (Table-III).

Table-I: Demographic characteristic of the patients (n=60)

Demographic variables		**Group I (n=30)**	**Group II (n=30)**
Age (in years)		41.13±9.63	38.63±9.82
Weight (in Kg)		65.53±8.21	63.77±8.14
ASA	**class I**	18(60%)	22(73.3%)
	class II	12(40%)	8(26.7%)
Sex	**Male**	19(63.3%)	23(76.7%)
	Female	11(36.7%)	7(23.3%)

Table-II: Incidence of fasciculation between two groups (n=60)

Fasciculation grade	**Group I (n=30)**	**Group II (n=30)**	**P value**
0-No fasciculation	4 (13.3%)	2 (6.7%)	0.001[s]
1-Mild	18 (69.2%)	5 (17.9%)	
2-Modarate	6 (23.1%)	19 (67.9%)	
3-Severe	2 (7.7%)	4 (14.3%)	

s=significant

Mean serum potassium level 5 minutes before succinylcholine administration was 4.19±0.39 mmol/L and 4.06±0.22 mmol/L, while after 5 minutes of succinylcholine administration was found 4.24±0.41 mmol/L and 4.41±0.24 mmol/L in group I and group II respectively. The rise of serum potassium level in group I was 0.05±0.02 mmol/L and in group II was 0.35±0.02 mmol/L. This rise of serum potassium level was lower in group I and it was statistically significant (P=0.055) (Table-IV). In the zero post-operative hour, VAS score of group I was 5.10 ±1.47 and group II was 6.67±1.81 which was statistically significant (P=0.001). After 4 hours of post-operative period, VAS score of group I and group II were 3.17±1.32 and 4.60±2.13 respectively. After 8 hours of post-operative period, VAS scores were 3.33±1.18 and 5.27±2.24 respectively and the difference was statistically significant. However, in other observations such as 4, 12, 16, 20 and 24 postoperative hours, VAS scores between the groups were not significant statistically (P>0.05) (Table-V). The mean total morphine consumption was 11.18±3.77 mg in group I and 18.28±7.95 mg in group II. This difference was statistically significant. Morphine consumption was significantly high in group II patients (P=0.001) (Table-VI).

Table-III: Incidence of myalgia between two groups (n=60)

Myalgia grade	**Group I (n=30)**	**Group II (n=30)**	**P value**
0-No	13 (43.3%)	5(16.7%)	0.022[s]
1-Mild	12 (70.6%)	7(28.0%)	
2-Moderate	4(23.1%)	16(64.0%)	
3-Severe	1(5.9%)	2(8%)	

s=significant

Table IV: Serum potassium levels before and after administration of succinylcholine between two groups (n=60)

Serum potassium level (mmol/L)	**Group I (n=30)**	**Group II (n=30)**	**P value**
5 minutes before	4.19± 0.39	4.06± 0.22	0.001[s]
5 minutes after	4.24± 0.41	4.41± 0.24	
Mean rise	0.05± 0.02	0.35± 0.02	

The result was shown as mean±SD; s=significant

The mean first analgesic demand was 3.69±0.54 hours in group I and 2.19±0.49 hours in Group II; the difference was statistically significant (P=0.001) (Table-VI).

Table-V: VAS score in the post-operative room between two groups (n=60)

Points of time	Group I (n=30)	Group II (n=30)	P value
0 hour	5.10±1.47	6.67±1.81	0.001[s]
4 hours	3.17±1.32	4.60±2.13	0.002[s]
8 hours	3.33±1.18	5.27±2.24	0.001[s]
12 hours	2.43±1.48	3.17±2.13	0.105[ns]
16 hours	2.33±1.24	2.73±1.48	0.261[ns]
20 hours	1.40±0.67	1.43±0.57	0.852[ns]
24 hours	1.10±0.31	1.10±0.40	1.000[ns]

The result was shown as mean±SD; s=significant, ns=not significant

Table-VI: Total morphine requirement (mg) and Time of first analgesia demand (morphine) between two groups (n=60)

Variables	Group I (n=30)	Group II (n=30)	P value
Total morphine requirement (mg)	11.18± 3.77	18.28± 7.95	0.001[s]
Time of first analgesia demand (morphine)	3.69± 0.54	2.19±0.49	0.001[s]

The result is shown as mean±SD; s=significant.

Discussion

Patients for elective spine surgery under general anaesthesia were recruited for this prospective, randomized control trial. Oral pregabalin 150 mg was given to trial group and matching placebo was given to control group one hour before surgery. This study carried out with the aims to evaluate the effect of pregabalin 150mg on succinylcholine induced adverse effect like fasciculation, myalgia, and hyperkalaemia.

In this study, patients with elective spine surgery under general anaesthesia, it was found that use of prophylactic pregabalin 150 mg could not reduce the incidence of fasciculation; however, it reduced the severity of fasciculation. Abbas *et al.*[1] studied with rocuronium pretreatment one minute prior to induction and found rocuronium reduced fasciculation. Srivastava *et al.*[2] and Khan *et al.*[3] studied with pregabalin 150 mg to reduce succinylecholine induced fasciculation in different surgery and showed that pregabalin reduced the severity without having any effect on its incidence. In a different study, Mencke *et al.*[10] showed that pretreatment with rocuronium significantly reduced incidence and severity of fasciculation.

In this study, prophylactic pregabalin 150 mg significantly reduced both the incidence and severity of postoperative myalgia. Srivastava *et al.*[2] and Khan *et al.*[3] studied with pregabalin 150 mg and got similar effects. Rajappa *et al.*[11] also found that preoperative pregabalin 150 mg effectively reduced postoperative pain. Alimian *et al.*[12] also concluded that pregabalin reduces postoperative pain. Our study found that mean serum potassium level was increased more in control group and pregabalin can reduce the rise of potassium level. Magee *et al.*[13] showed that increase serum potassium concentration can occur even after single paralyzing dose of suxamethonium. Ahsan *et al.*[14] studied with magnesium sulphate and normal saline and

concluded that magnesium sulphate can significant lower the potassium level after anaesthesia. Stacey *et al.*[15] used magnesium sulphate pretreatment and showed that serum potassium concentration was almost similar between two groups. Yun *et al.*[16] found similar potassium levels in both groups. The difference may be due to the use of different pretreatment agents. Shafy *et al.*[17] and Collier[18] reported that serum potassium concentration increased in patients who develop myalgia after succinylcholine administration.

We also found a reduction in post-operative VAS score throughout the study period which was significant in 0, 4 and 8 hours. Kim *et al.*[19] studied effect of pregabalin on post-operative pain after mastectomy and found VAS scores were significantly lower in pregabalin group as compared to placebo group in initial 8 hours. Jadeja *et al.*[20] also found that pregabalin reduced pain score (VAS) especially after 1 and 4 hours. Balaban *et al.*[21] studied randomized placebo-controlled trial of pregabalin on post-operative pain intensity after laparoscopic cholecystectomy and concluded that post-operative pain scores were significantly lower in pregabalin group as compared to placebo group. The difference in results may be due to variations in pain intensities depending on the nature of surgery and form (whether it is visceral or somatic).

In the present study, total opioid (morphine) requirement was less in pregabalin group than the control group which was statistically significant. Srivastava *et al.*[2] and Baidya *et al.*[22] also reported that pregabalin can reduce opioid consumption in the first 24 hour of surgery. Jadeja *et al.*[20] and Agarwal *et al.*[23] found that pregabalin reduced postoperative pain and analgesic (NSAIDs) requirement. Moreover, Alimian *et al.*[12] found that pregabalin can reduce postoperative opioid consumption, too.

Conclusion

Pretreatment with single dose of 150 mg of pregabalin an hour before surgery can be used to reduce succinylcholine induced adverse effects like fasciculation, myalgia and hyperkalaemia. It also reduces postoperative opioid consumption.

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