

Comparison of the Effect of Pretreatment with Cisatracurium and Rocuronium on Succinylcholine Induced Fasciculation for Patients undergoing Surgery under General Anaesthesia: A Randomised Clinical Study

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ABSTRACT

Introduction: Succinylcholine is the best agent for providing ideal intubating condition. Muscle fasciculation is common after succinylcholine administration and causes postoperative myalgia. Pretreatment with non depolarising muscle relaxant decreases fasciculation and myalgia after succinylcholine administration.

Aim: To compare the efficacy between cisatracurium and rocuronium in preventing succinylcholine induced fasciculation in patients undergoing general anaesthesia and determining association between fasciculation and myalgia after succinylcholine use.

Materials and Methods: The present study was a hospital-based, randomised, double-blinded clinical study conducted from January 2020 to July 2020. The study included 64 patients of American Society of Anaesthesiologists (ASA) grade I and II undergoing surgery under general anaesthesia which were randomly allocated in two groups. Group 1 (N=32) received intravenous (i.v.) cisatracurium (0.01 mg/kg) and group 2 (N=32) received i.v. rocuronium (0.06 mg/kg) as precurarising agent, three minutes before i.v. succinylcholine

(1.5 mg/kg) administration. Incidence and intensity of fasciculation after succinylcholine injection was observed using a 4 point scale. Haemodynamic parameters were compared by measuring Mean Arterial Pressure (MAP) and Heart Rate (HR) before and after intubation. Patients were followed-up in Postanesthesia Care Unit (PACU) on Postoperative Day 1 (POD1) for myalgia. Observations in two groups were analysed using standard statistical test.

Results: Fasciculation was significantly lower in group 2 (mean 0.2187 ± 0.4200) than group 1 (mean 1.125 ± 0.833 , p-value < 0.001). A significant association was found between fasciculation after succinylcholine injection and postoperative myalgia (p-value=0.007). Group 2 had less incidence of myalgia than group 1. However, the difference was not statistically significant.

Conclusion: Rocuronium was more efficacious than cisatracurium in preventing succinylcholine induced fasciculation and rocuronium was more effective in preventing succinylcholine-related postoperative myalgia.

Keywords: Non depolarising muscle relaxant, Precurarisation, Postoperative myalgia

INTRODUCTION

Succinylcholine is the only available depolarising muscle relaxant for clinical use with rapid onset and ultra short duration of action [1]. It is popularly used to achieve profound neuromuscular blockade providing ideal condition for tracheal intubation. Succinylcholine is two molecules of acetylcholine combined. This structure underlies succinylcholine's mechanism of action, side-effects, and metabolism [2]. Its use is associated with a number of undesired side-effects, e.g; muscle fasciculation and postoperative myalgia; which though not potentially life-threatening, but causes significant discomfort in some patients.

Fasciculation refers to visible muscle contractions resulting from asynchronous firing of all the muscle fibres in a motor unit supplied by a motor neuron [1]. Muscle fasciculations are common after succinylcholine administration which are attributed to antidromically conducted axonal depolarisations initiated by the agonist action of succinylcholine on prejunctional nicotinic receptors at the neuromuscular junction [3]. Fasciculations after succinylcholine administration have been associated with postoperative myalgia [4]. Incidence of muscle pain after succinylcholine injection varies from 0.2-89% [1] and is more frequent in minor, ambulatory surgeries and in women. The relationship between fasciculation and postoperative myalgia is inconsistent. Myalgias are theorised to be due to initial unsynchronised contraction of muscle groups [2].

Several methods have been instituted to prevent or reduce the incidence of fasciculation after succinylcholine administration including pretreatment with lidocaine/diazepam/phenytoin/sub-paralysing doses of Non Depolarising Muscle Relaxant (NDMR). Perioperative Non Steroidal Anti-Inflammatory Drugs (NSAIDs) and benzodiazepines may reduce incidence and severity of myalgia [2]. Preliminary evidence shows that precurarisation with small dose of NDMR suppresses fasciculation. The NDMR given before succinylcholine will bind to presynaptic neuronal nicotinic acetylcholine receptor and block binding of succinylcholine, therefore reducing fasciculation. Role of rocuronium has been extensively studied for the purpose and shown efficacy for defasciculation at dosage of 0.06-0.1 mg/kg [2].

Cisatracurium is a comparatively newer NDMR which is four or five times more potent than atracurium [1]. It is one of the ten isomers of atracurium and constitutes 15% of the mixture. It is noted to have less production of laudonosine, devoid of histamine releasing property and autonomic effects even at very high doses (almost eight times of ED₉₅ i.e., the dose causing on average 95% suppression of neuromuscular response) [2] with significantly lesser cardiovascular side-effects. To suppress fasciculation in patients undergoing surgery under general anaesthesia, present study have compared efficacy of these two NDMR- cisatracurium and rocuronium.

The primary objective of the study was to determine the comparative efficacy between cisatracurium and rocuronium in preventing succinylcholine induced muscle fasciculation in patients undergoing surgery under general anaesthesia. Secondary objective was to find out any possible association between fasciculation and postoperative myalgia in patients receiving succinylcholine, to determine efficacy of NDMRs in preventing such muscle aches and also to associate the haemodynamic changes reflected after intubating dose of succinylcholine within the study groups.

MATERIALS AND METHODS

The present study was a hospital-based, randomised, double-blinded clinical study, conducted from January 2020 to July 2020 in the elective surgery operating room of a tertiary care centre. Clearance from the Institutional Ethics Committee (IEC) (Letter number: RKC/114, Dated: 12.02.2020) was obtained.

Inclusion criteria: A sample of 64 adult patients of ASA grade I and II (aged 18-65 years) were enrolled in this study.

Exclusion criteria: Patients with morbid obesity, history of neuromuscular disease, history of cardiovascular/renal/hepatic disease, suspected difficult intubation, pregnancy, raised intracranial tension/intraocular tension, hyperkalaemia, burn patients were excluded from the study.

Sample size calculation: Sample size for the study was calculated based on a previous study conducted by Joshi GP et al., [5] by applying the formula:

$$\text{Sample size (n)} = \frac{(p_0q_0 + p_1q_1)(z_{1-\alpha/2} + z_{1-\beta})^2}{(p_1 - p_0)^2}$$

p_0 = Success rate in cisatracurium group.

p_1 = Success rate in rocuronium group.

Applying the formula,

$$n = \frac{(0.7 \times 0.3 + 0.95 \times 0.05) \times 7.84}{(0.95 - 0.7)^2}$$

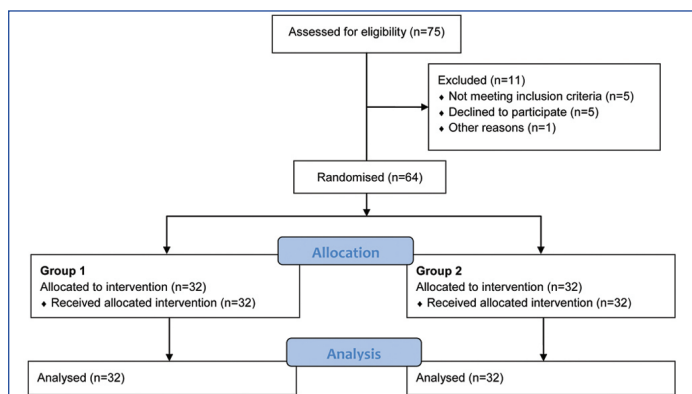
$$= 32.23$$

= 32 (Approximately)

So, sample size in each group was 32, total sample size was 64. Statistical power was 80%. Fasciculation of less than grade 2 was defined as effective pretreatment.

Procedure

The enrolled patients were randomly allocated by a computer generated randomisation table, in a double blinded manner, to one of the two groups- group 1 (N=32) and group 2 (N=32) [Table/Fig-1]. Detailed written informed consent was obtained from all the participants. However, the participants were not informed about the group distribution and which drug to be administered to them.



[Table/Fig-1]: Flowchart of the study plan.

A standardised anaesthesia protocol was implemented for all participants. On the day of surgery, patients in the operating room were attached with standard ASA monitors. Preoperative HR and

MAP were recorded. Patients were preoxygenated with 100% oxygen for three minutes. Then the patients were injected with i.v. midazolam (0.03 mg/kg), i.v. fentanyl (2 µg/kg) and i.v. glycopyrrolate (4 µg/kg). Group 1 received pretreatment with i.v. cisatracurium at 0.01 mg/kg and group 2 received pretreatment with i.v. rocuronium at 0.06 mg/kg. Study solutions (a standardised volume of 3 mL) [5] were prepared by a senior resident, who was given a written protocol for drug preparation. Anaesthesiologist who administered the drug and recorded the data was unaware of the composition of the solution administered. Patients were monitored for three minutes for any clinical sign of muscle weakness like eye weakness, diplopia etc. During this time, patients were oxygenated with 100% oxygen. After three minutes, general anaesthesia was induced with i.v. propofol (2 mg/kg), i.v. succinylcholine was given at 1.5 mg/kg. Intensity of fasciculation was assessed using the Harvey Scale [6] with 4 point rating from 0-3 as follows [Table/Fig-2].

Grades	Intensity of fasciculation
0 (No)	No fasciculation
1 (Mild)	Mild, fine fasciculations of eyes, neck, face, fingers without limb movement.
2 (Moderate)	Moderate fasciculations occurring at more than 2 sites or obvious limb movements.
3 (Severe)	Vigorous or severe sustained and widespread fasciculations in the trunk and limb.

[Table/Fig-2]: Harvey Scale with 4 point rating [6].

Airway was secured one minute after succinylcholine administration. Postintubation HR and MAP were recorded. All the participants received inj. fentanyl (2 µg/kg) before induction, inj. diclofenac (1 mg/kg) intraoperatively, inf. paracetamol (15 mg/kg) just before extubation and inj. paracetamol (15 mg/kg) eight hourly in the postoperative period for analgesia. The patients were followed-up on postoperative day one and were enquired about presence of muscle aches. Patients who complained of myalgia were administered i.v. paracetamol infusion (1 g), as rescue analgesic.

STATISTICAL ANALYSIS

Data was entered into Microsoft Excel spreadsheet and analysed using parametric and non parametric tests and Statistical Package for the Social Sciences (SPSS) version 23.0. Categorical data were presented as numbers (n) and percentage (%) and compared using Chi-square test. Numerical data were presented as mean and standard deviation (mean±SD) and evaluated using unpaired t-test. A p-value <0.05 was considered for statistical significance.

RESULTS

[Table/Fig-3] shows that the two groups were comparable for age, sex, weight, height. [Table/Fig-4] shows incidence of significant fasciculation (Fasciculation Grade ≥ Grade 2 was considered significant) in the 2 groups. It revealed that group 2 has less occurrence of significant fasciculation than group 1 and the value was statistically significant (p-value <0.001).

Parameters	Mean±SD		p-value
	Group 1	Group 2	
Age (years)	44.0±12.0	47.0±11.0	0.350
Sex (Male/Female)	23/9	15/17	0.420
Weight (kg)	61.0±9.0	64.0±9.0	0.408
Height (cm)	146.0±4.0	146.0±4.0	0.903

[Table/Fig-3]: Demographic data analysis.

Parameter	Group 1	Group 2	p-value
Fasciculation (Mean±SD)	1.125±0.833	0.2187±0.4200	<0.001

[Table/Fig-4]: Occurrence of fasciculation.

A p-value <0.05 is considered to be statistically significant

[Table/Fig-5] shows the difference of occurrence of fasciculation according to severity grading between the two groups. Most patients of group 1 had mild to moderate fasciculation (23 out of 32), one patient had severe fasciculation and eight patient had no fasciculation. Where as in group 2, fasciculations did not occur in most of the patients (25 out of 32) and seven patients had mild fasciculation. Moderate or severe fasciculation did not occur in any patient of group 2.

Fasciculation grade		Group 1 n (%)	Group 2 n (%)	Total
0	Count (% within fasciculation grade)	8 (24.2)	25 (75.8)	33 (100)
1	Count (% within fasciculation grade)	13 (65.0)	7 (35.0)	20 (100)
2	Count (% within fasciculation grade)	10 (100)	0	10 (100)
3	Count (% within fasciculation grade)	1 (100)	0	1 (100)
Count (% of total)		32 (50)	32 (50)	64 (100)

[Table/Fig-5]: Occurrence of fasciculation according to severity grading.

[Table/Fig-6] shows that the patients in group 2 had less incidence of myalgia (on postoperative day 1) than group 1. But, the difference was not statistically significant. Data in [Table/Fig-7] shows that incidence of myalgia was related to occurrence of fasciculation after succinylcholine injection. This relation was statistically significant.

Groups	No		Yes		Total	p-value	
	Count (% of total)	Count (% within group)	Count (% of total)	Count (% within group)	Count (% of total)	Total	Within group
Group 1	18 (28.1)	18 (56.25)	14 (21.9)	14 (43.75)	32 (50)	0.069	0.062
Group 2	25 (39.0)	25 (78.12)	7 (11)	7 (21.88)	32 (50)		
Total	43 (67.1)	43 (67.1)	21 (32.9)	21 (32.9)	64 (100)		

[Table/Fig-6]: occurrence of myalgia between two groups on postoperative day 1.

Myalgia	Fasciculation		Total
	Yes (Grade >1)	No (Grade <2)	
Yes	9	12	21
No	2	41	43
Total	11	53	64

p-value=0.00014

[Table/Fig-7]: Relationship between myalgia and fasciculation.

A p-value <0.05 is considered to be statistically significant

[Table/Fig-8] shows that myalgia (on POD1) occurred in 18.19% patients (15.15% patients were from group 2) who had no fasciculation, in 30% patients (20% belongs to group 1) having

Fasciculation grade	Myalgia on POD1			Total Count (% of total)
	No	Yes	Count (% within grade) n (%)	
	Count (% within grade) n (%)	Count (% within grade) n (%)		
Grade 0	Group 1	7 (21.21)	1 (3.03)	33
	Group 2	20 (60.61)	5 (15.15)	
	Total	27 (81.81)	6 (18.19)	
Grade 1	Group 1	9 (45)	4 (20)	20
	Group 2	5 (25)	2 (10)	
	Total	14 (70)	6 (30)	
Grade 2	Group 1	2 (20)	8 (80)	10
	Group 2	0	0	
	Total	2 (20)	8 (80)	
Grade 3	Group 1	0	1 (100)	1
	Group 2	0	0	
	Total	0	1 (100)	
Total		43	21	64

p-value=0.007

[Table/Fig-8]: Relationship between occurrences of myalgia with severity of fasciculation.

A p-value <0.05 is considered to be statistically significant

mild fasciculation, in 80% patients (all from group 1) with moderate fasciculation and in 100% patients (from group 1) with severe fasciculation. So, it is concluded that those having myalgia also had fasciculation and the value is statistically significant (p-value=0.007). Total 21 patients experienced myalgia on POD1 and were administered rescue analgesic.

[Table/Fig-9a] shows that preinduction HR and preinduction MAP between group 1 and group 2 were comparable. Comparing postintubation HR at 5 minutes with preinduction values [Table/Fig-9b], it was found that in patients receiving cisatracurium (group 1) the change in HR before and after intubation was not statistically significant. However, HR at 5 minutes after intubation significantly increased in rocuronium group (group 2). Statistically significant increase in postintubation MAP was found in group 1 in contrast to group 2 where the difference of preinduction and postintubation mean MAP was insignificant [Table/Fig-9b].

DISCUSSION

Succinylcholine has been the most suitable neuromuscular blocking drug to provide ideal conditions for endotracheal intubation in majority of the general anaesthesia cases [1]. But in recent years anesthesiologists are avoiding it because of the side-effects such

Parameters	Mean±SD		p-value
	Group 1	Group 2	
Preinduction HR	89.0±19.0	87.0±17.0	0.861
Postintubation HR at 5 minute	94.22±18.81	92.38±12.18	0.328
Preinduction MAP	76.09±8.00	78.84±10.00	0.591
Postintubation MAP at 5 minute	81.34±10.43	80.38±10.32	0.500

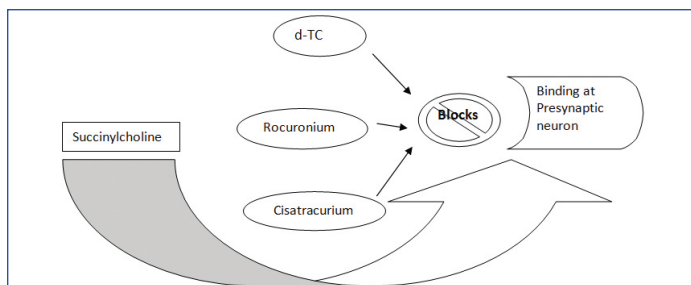
[Table/Fig-9a]: Comparison of preinduction and postintubation (at 5 minutes) HR and MAP between the 2 groups.

Parameters	Group 1		Group 2	
	Mean±SD	p-value	Mean±SD	p-value
Preinduction HR	88.78±19.051	0.097	86.63±16.831	0.0412*
Postintubation HR at 5 minute	94.22±18.811		92.38±12.175	
Preinduction MAP	76.06±7.997	0.0173*	78.84±9.997	0.4862
Postintubation MAP at 5 minute	81.34±10.434		80.38±10.320	

[Table/Fig-9b): Comparison between preinduction and postintubation (at 5 minutes) HR and between preinduction and postintubation MAP within the same group. *p-value <0.05 is considered to be statistically significant

as fasciculations, postoperative myalgia, and rise in potassium level etc. But, because of its cost-effectiveness and easy availability, it is still being used in many developing countries. Hence many studies are still going on to minimise its side-effects. Most popular agent to reduce succinylcholine related fasciculation which is attributed to prejunctional depolarising action of succinylcholine [1], is small dose of NDMR. NDMR given before succinylcholine, will bind to presynaptic nicotinic neuronal acetylcholine receptor, therefore fasciculations should be reduced or prevented [7] [Table/Fig-10].

A meta-analysis of clinical trials for prevention of postoperative myalgia due to succinylcholine discovered that administration of pretreatment dose of various non depolarising blockers reduced the incidence and severity of fasciculations and myalgia by approximately 30% [8]. In another meta-analysis of randomised trials, it was noted



[Table/Fig-10]: Site of binding of succinylcholine to the presynaptic neuronal acetylcholine receptors and action of NDMRs blocking such binding.

that the incidence of succinylcholine-induced myalgia is high and symptoms sometimes lasted for several days. It was also found that small doses of NDMRs (i.e. approximately 10-30% of ED95) prevent fasciculation and myalgia to some extent; however, the risk of potentially serious adverse effects is not negligible [9].

Joshi GP et al., in a study conducted to show effects of pretreatment with cisatracurium, rocuronium and d-Tubocurarine on succinylcholine-induced fasciculations and myalgia, had demonstrated that both rocuronium and d-tubocurarine were superior to cisatracurium in preventing succinylcholine induced fasciculation. In the aforesaid study, although fasciculations were observed less frequently in the cisatracurium group (compared to placebo), this difference did not reach statistical significance [6].

In another similar study done by Cybil AT et al., statistically significant difference was demonstrated between rocuronium and cisatracurium fasciculation scores (p -value=0.001) where rocuronium was more effective in preventing succinylcholine-induced fasciculations. The study also found that cisatracurium at a dose of 0.02 mg/kg was not effective for defasciculation [7]. Kothari D et al., assessed and compared the effect of pretreatment with rocuronium and Vecuronium on postsuccinylcholine fasciculations, rise in serum potassium and Postoperative myalgia and they also concluded that Rocuronium is more effective in preventing postsuccinylcholine fasciculations, rise in serum potassium and Postoperative myalgia [10].

In present study, it was found that rocuronium was superior to cisatracurium in preventing succinylcholine induced fasciculation. This finding supports the observation done by Mencke T et al., [11] which also showed that rocuronium was superior to cisatracurium in preventing succinylcholine induced fasciculation compared to saline. Present study observation also matches the study done by Motamed C et al., [12] which showed that rocuronium prevents succinylcholine induced fasciculation. One of the reasons for the differences in the efficacy of these two NDMRs for defasciculation may be related to their affinity for prejunctional acetylcholine receptors [13]. It is suggested that NDMRs with greater affinity for these receptors (e.g-rocuronium) are highly efficacious for defasciculation. Other reason for lesser efficacy of cisatracurium may be related to its slower onset of action [6]. In present study three minutes interval between the defasciculating dose of cisatracurium and succinylcholine administration was given. It is possible that a longer interval between the defasciculating dose of cisatracurium and succinylcholine may have improved the effectiveness of cisatracurium in preventing fasciculation. This observation was supported by a study conducted by Mencke T et al., [14] to show the influence of precurarising interval in case of precurarisation with cisatracurium where they found that incidence of muscle fasciculation was reduced when a longer pretreatment interval (i.e., 6 minutes, instead of 3 minutes) was chosen. The study done by Kim JH et al., on optimal precurarising dose of rocuronium to decrease fasciculation and myalgia also showed same result [15].

An optimal pretreatment interval of three minutes has been recommended for many commonly used NDMR for defasciculation. Such a lengthy interval may pose the awake patient at risk of unpleasant experience of muscle weakness, difficulty in breathing

and swallowing. To avoid this hazard, many have chosen a shorter precurarising interval as reported in a study done by Findlay GP and Spittal MJ, where they had used 60 seconds interval between pretreatment dose of rocuronium and succinylcholine. Due to rapid onset of action of rocuronium, such short interval was acceptable [16]. But, as cisatracurium has a longer onset of action, present study chose the standard recommendation of three minutes precurarising interval for both the drugs and no side-effects were noted.

Efficacy of precurarisation technique also depends on the pretreatment dose. An optimal pretreatment dose should be adequate to be efficacious without producing any side-effects. With defasciculating dose of NDMR exceeding 20% of the ED95 or 10% of the standard intubating dose, side-effects like heavy eyelids, diplopia, swallowing difficulty and generalised discomfort may occur. Even there is chance of respiratory compromise and dyspnoea, however incidence is rare. Aspiration of gastric contents after administration of defasciculating dose of NDMR also has been reported [17,18]. Therefore considering safety of the study population, present study have used both the NDMRs at a dose of 20% of ED95 i.e., cisatracurium at a dose of 0.01 mg/kg and rocuronium at a dose of 0.06 mg/kg.

In a previous study conducted by Fukano N et al., a pretreatment dose of i.v. rocuronium at 0.06 mg/kg body weight before succinylcholine resulted in depression of an average TOF ratio from 100 to 68% [19]. In another study, Martin R et al., [20] observed ocular side-effects in 90% of the patients receiving pretreatment with mivacurium, 20% complained of difficulty in swallowing along with inability to sustain head lift for more than four seconds and 10% of the patients complained of respiratory discomfort. However, these investigators did not find any correlation between the magnitude of side-effects and prevention of fasciculation. In present study, no patients amongst the study population had developed side-effects related to the pretreatment drug.

The relationship between fasciculation and postoperative myalgia is not well-defined [14]. Succinylcholine induced fasciculation is widely believed to be the primary cause of myalgia which is most common in the first postoperative day [21]. Pretreatment decreases the incidence of fasciculations, but the severity of fasciculation is not related with frequency of postoperative myalgia [22]. Rocuronium was found effective in preventing muscle fasciculation, but did not prevent postoperative myalgia [5]. Another study by Martin R et al., also failed to conclude about decrease of postoperative myalgia with the use of pretreatment. But it successfully demonstrated the efficacy of rocuronium at a dose 0.06 mg/kg in preventing succinylcholine induced fasciculation [20]. In present study, the relation between fasciculation and postoperative myalgia on POD1 was found to be statistically significant, though no significant association was found with grades of fasciculation and myalgia. Present study also observed that incidence of myalgia was less in rocuronium group than cisatracurium group, however, this difference did not reach statistical significance.

One of the concerns regarding pretreatment with NDMR is that, efficacy of succinylcholine may be reduced resulting in adverse intubating conditions [23]. A study showed that subparalysing doses of NDMR did not affect intubating conditions after succinylcholine at a dose 1.5 mg/kg. McLoughlin C et al., [23] reported that increasing the dose of succinylcholine did not increase the incidence of side effects. So, to achieve ideal intubating condition, succinylcholine has been used at a dose of 1.5 mg/kg in present study.

In this study, the preinduction Heart Rate (HR) and Mean Arterial Pressure (MAP) were noted and compared with postintubation values at 5 minutes in the two groups. HR at 5 minutes after intubation significantly increased in rocuronium group (group 2). This could be explained by the vagolytic property of rocuronium [24] causing increase in HR in the subjects of group 2. MAP at 5 minutes after intubation increased in cisatracurium group (group 1) which was not clinically significant and no intervention was needed (A significant

increase in blood pressure is defined as an increase in systolic BP of greater than 20 mmHg, diastolic BP of greater than 10 mmHg or initiation of antihypertensive medication) [25].

Limitation(s)

Present study was a single centre study. Multicentre study with larger sample size in future will be better to establish the results. Also, effect of pretreatment with cisatracurium and rocuronium on the rise of serum potassium after succinylcholine administration was not investigated.

CONCLUSION(S)

The study showed that pretreatment with rocuronium at 0.06 mg/kg is more effective than cisatracurium at a dose 0.01 mg/kg in preventing succinylcholine induced fasciculation. There was a positive association between fasciculation and myalgia. Rocuronium showed better efficacy in preventing postoperative myalgia in patients receiving succinylcholine in present study.

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AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

PLAGIARISM CHECKING METHODS: [Jan H et al.]

- Plagiarism X-checker: May 04, 2022
- Manual Googling: Jul 07, 2022
- iThenticate Software: Aug 29, 2022 (15%)

ETYMOLOGY: Author Origin

Date of Submission: **Apr 27, 2022**
Date of Peer Review: **May 30, 2022**
Date of Acceptance: **Jul 09, 2022**
Date of Publishing: **Sep 01, 2022**