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Effect of pre-treatment with rocuronium and vecuronium on post succinylcholine fasciculations, serum potassium, and postoperative myalgia: A prospective, randomized, double-blind study

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ABSTRACT

Background: Succinylcholine with quick onset, ultra short duration of action, and complete predictable paralysis has been the best drug for endotracheal intubation but the occurrence of side effects such as muscle fasciculations, postoperative myalgia, rise in serum potassium levels and myoglobinuria limits its use in the full stomach, burns, massive trauma, metabolic acidosis, and few myopathies. For attenuation of these effects, many drugs have been studied but pre-treatment with non-depolarizing muscle relaxant found to be successful. **Aims and Objectives:** This study was designed to assess the effect of Rocuronium and Vecuronium pre-treatment on post-succinylcholine fasciculations, rise in serum potassium levels, and postoperative myalgia. **Materials and Methods:** 100 patients between the age of 20–50 years of either sex (American Society of Anaesthesiologists grade I and II) undergoing general anesthesia for various surgical procedures were randomly allocated into two groups according to pre-treatment with Rocuronium (Group R) and Vecuronium (Group V) before Succinylcholine administration. After Succinylcholine administration severity of fasciculations, rise in serum potassium after 5 min and myalgia on postoperative days 1, 2, and 3 were recorded. **Results:** About 74% patients had no fasciculation in Group R as compared to 36% in group V. Statistically insignificant ($P > 0.05$) rise in serum potassium level was observed in both groups. Higher number of patients had mild-to-moderate degree of myalgia with Vecuronium on postoperative days 2 and 3. **Conclusion:** Pre-treatment with Rocuronium before Succinylcholine provided better attenuation of post-succinylcholine muscle fasciculations, postoperative myalgia with statistically insignificant rise in serum potassium levels.

Key words: Fasciculations; Myalgia; Potassium; Pre-treatment; Rocuronium; Vecuronium

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INTRODUCTION

The introduction of neuromuscular blocking drugs made a conceptual change in the practice of general anesthesia. Laryngoscopy and endotracheal intubation is commonly facilitated with Succinylcholine, a depolarizing muscle relaxant that offers excellent intubation conditions within 30–60 s and its effect lasts for 3–5 min.[1]

Succinylcholine being cost-effective with quicker onset of action, shorter duration of action, and complete predictable paralysis remains the best drug in providing ideal conditions for endotracheal intubation in the majority of the cases.[2]

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However, the utility of succinylcholine is restricted by frequent well-described incidences of side effects such as rise in intracranial pressure, intraocular pressure, intragastric pressure, muscle fasciculations, postoperative myalgia rise in serum potassium levels, and myoglobinuria.

In 1.5–89% of cases the Succinylcholine induced fasciculations cause postoperative myalgia in the muscles of the neck, shoulder, back and upper abdomen, commonly after 24–48 h, which usually last for 2–3 days to maximum of 7 days.[3,4] Post-fasciculation rise in serum potassium level could be deleterious in certain cases like severe burns, massive trauma, metabolic acidosis, myo-neuropathies.

Different drugs have been studied to attenuate these undesirable effects associated with succinylcholine such as pre-treatment with Gallamine,[5] d-Tubocurarine,[5] Dantrolene,[6] Phenytoin,[7] Pancuronium,[8] Atracurium,[9] Lidocaine,[9] Ascorbic acid,[10] Chlorpromazine,[11] Aspirin,[11] Magnesium sulfate,[12] Calcium gluconate,[13] Diazepam,[14] Midazolam.[15] Out of all, Non-depolarizing neuromuscular relaxant (NDMR) drugs have been found most effective in attenuation of these side effects.[16-23]

Aims and objectives

The present clinical study was conducted to assess and compare the effect of pre-treatment with Rocuronium and Vecuronium on post succinylcholine fasciculations, rise in serum potassium, and post-operative myalgia.

MATERIALS AND METHODS

This prospective comparative single center clinical study was pre-approved by the Institutional Ethics Committee (IEC) for the final permission (vide letter no. 125-140/Bio/Ethical/MC/03/13). After obtaining the permission of IEC the study was conducted in a medical college hospital of central India. Well-informed written consent was obtained from the selected patients over the period of 1 year.

Inclusion criteria

Patients between the ages of 20–50 years of both sexes with American Society of Anaesthesiologists-I/II, scheduled for elective lumbar spine surgery under general anesthesia necessitating laryngoscopy and endotracheal intubation were enrolled for this study to maintain uniformity and to avoid effect of surgery-related factors on postoperative myalgia.

As calculated from a previous study[16-20] to get a clinically relatable variation in the serum potassium levels, 50 patients were required in each of the groups with a power of study 80% at 95% confidence interval (alpha=0.05). A total number of patients=100; they were randomly assigned into two groups (n=50, each) using an online randomization tool.

Exclusion criteria

Patient refusal, pregnant and lactating mothers, significant neurological, endocrinal, hepatic or renal dysfunction, patients susceptible to Succinylcholine induced hyperkalemia as mentioned in introduction.

Computer-generated randomization technique was followed to divide the enrolled 100 patients into two groups as below:

- Group R - Received Inj. Rocuronium (0.06 mg/kg I/V), 60 s before Succinylcholine
- Group V - Received Inj. Vecuronium (0.01 mg/kg I/V), 60 s before Succinylcholine.

All the patients underwent detailed pre-anaesthetic assessment and investigations as per hospital protocol. All the patients were kept nil orally for 6 h before procedure. Upon arrival of patient in the operation room, basal pulse rate (bpm), blood pressure (mmHg), SpO_2 (%) were measured and recorded. A venous blood sample was collected before induction of anesthesia for estimation of serum potassium level. Then Normal Saline infusion was started @ 10–15 drops/min. After premedication with Injection. Glycopyrrolate 0.2 mg I.V. and Injection. Pentazocin 0.5 mg/kg BW and pre-oxygenation with 100% Oxygen for 3 min by facemask, pre-treatment was done with either of the study drug (the anesthetist on floor and researcher were unaware of the injection of study drug). After 60 s of pre-treatment general anesthesia was induced with injection. Thiopentone Sodium 5 mg/kg BW. Tracheal intubation was facilitated with intravenous injection. Succinylcholine 2.0 mg/kg BW. Observer noted the presence and severity of muscle fasciculations.[24]

- Grade 0 - No fasciculations
- Grade 1 - Fine fasciculations of the eyes, neck, face, or fingers without limb movements
- Grade 2 - Moderate fasciculations occurring at more than two sites or obvious limb movements
- Grade 3 - Vigorous or severe, sustained, and widespread fasciculations.

After endotracheal intubation general anesthesia was maintained on N_2O and O_2 (66%:33%) with Halothane (0.5 MAC) and Injection. Vecuronium loading (0.1 mg/kg BW) and intermittent (0.02 mg/kg BW) doses.

After 5 min of Succinylcholine administration, a second venous blood sample was taken for the estimation of serum potassium level. At the end of surgical procedure, residual effect of the muscle relaxant was reversed with

a combination of injection. Glycopyrrolate 0.01 mg/kg BW and injection. Neostigmine 0.05 mg/kg BW. After extubation and complete recovery, the patients were shifted to recovery room.

All the patients were interviewed by same observer on 1st, 2nd and 3rd postoperative days for occurrence and severity post-operative myalgia.[24]

- Mild - Muscle pain or stiffness at one site but not causing disability or limiting activities
- Moderate - Muscle pain or stiffness noticed spontaneously by the patient, possibly requiring analgesic therapy
- Severe - generalized severe or incapacitating discomfort.

Patients experiencing moderate to severe myalgia were injected Inj. Paracetamol 1 g, as rescue analgesia.

Statistical analysis

The observations were recorded and subjected to statistical analysis using student's "t" test and for qualitative variables chi-square test was used. The observations recorded in both the groups were tabulated and statistical analysis was carried out using appropriate statistical software. For intergroup comparison, P>0.05 and P<0.05 were considered as insignificant and significant, respectively.

RESULTS

Demographic data regarding the Age (years), Weight (kilograms), and Sex ratio (%) were comparable in both the study group (P>0.05) (Table 1). In group R, 74% patients had no fasciculation (Grade 0) as compare to 36% in group V (P=0.0001). Higher number of patients had Grade 1 and Grade 2 fasciculations in group V as compared to group R (50% vs. 24%) and (14% vs. 2%) respectively (P>0.05) (Table 2).

On 1st postoperative day, there was no difference between both the groups in terms of myalgia (P=184). On the 2nd and 3rd postoperative day, higher number of patients had either no myalgia or mild grade myalgia in Group V as compared to group R (P<0.05). Only few patients were experienced moderate grade myalgia among both the groups, which was found to be statistically not significant (Tables 3 and 4).

No significant rise in serum potassium was observed in both study groups (P=0.928) (Table 5).

DISCUSSION

Succinylcholine has been the most suitable neuromuscular blocking drug to provide ideal conditions for endotracheal intubation in majority of the general anesthesia cases.[2] But in recent years anesthetists are avoiding its use because of side effects such as fasciculations, postoperative myalgia, and rise in potassium level. Since being a cost-effective drug it is still used in many developing countries hence many studies are still done to minimize its side effects. A meta-analysis of clinical trials for prevention of postoperative myalgia due to succinylcholine discovered that administration of pre-treatment dose of various nondepolarizing blockers reduced the incidence and severity of fasciculations and myalgia by approximately 30%.[25]

In our study, the Rocuronium pre-treatment dose of 0.06 mg/kg was chosen which was approximately equipotent to 0.01 mg/kg of Vecuronium and <20% of ED_{95} hence safe and effective.[26] This was supported by the study conducted by Joshi et al.[26]

Waiting period between pre-treatment with nondepolarizing muscle relaxant and administration of succinylcholine

The effectiveness of nondepolarizing muscle relaxants in preventing succinylcholine-induced muscle fasciculations is highly dependent on the waiting time interval and choice of nondepolarizing drug.[8] There has been much discussion about the interval between the administration of the pre-treatment agent and succinylcholine. Interval of 2, 3, and 4 min or longer have been recommended.[27-29] The speed of onset of action of nondepolarizing relaxant at the postjunctional acetylcholine receptor has been shown to be inversely proportional to drug

Table 1: Demographic data

Parameters	Group R Mean (±SD)	Group V Mean (±SD)	P-value
Age (years)	34.98±8.26 Mean (±SD)	35.26±9.59 Mean (±SD)	0.876 (NS)
Weight (kg)	55.74±9.15 Mean (±SD)	56.80±7.32 Mean (±SD)	0.523 (NS)
Sex (M: F) (%)	52:48	56:44	0.689 (NS)

*NS: Non significant (P>0.05)

Table 2: Severity and inter-group statistical comparison of fasciculations in two study groups

Severity of fasciculations	Group-R		Group-V		Total		P-value
	(n)	(%)	(n)	(%)	(n)	(%)	
Grade-0	37	74	18	36	55	55	0.0001 (S)
Grade-1	12	24	25	50	37	37	0.007 (S)
Grade-2	1	2	7	14	8	8	0.028 (S)
Grade-3	-	-	-	-	-	-	-

*S: Significant (P<0.05)

Table 3: Severity of postoperative myalgia in two study groups

Severity of myalgia	1st P.O. Day*				2nd P.O. Day*				3rd P.O. Day*			
	Group R		Group V		Group R		Group V		Group R		Group V	
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
Nil	47	94	43	86	32	64	19	38	23	46	8	16
Mild	3	6	7	14	17	34	27	54	24	48	35	70
Moderate	-	-	-	-	1	2	4	8	3	6	7	14
Severe	-	-	-	-	-	-	-	-	-	-	-	-

*P.O.Day: Post-operative day

Table 4: Inter-group statistical analysis of severity of postoperative myalgia in two study groups

Severity of myalgia	1st P.O. Day	2nd P.O. Day	3rd P.O. Day
	P-value	P-value	P-value
Nil	0.184 (NS)	0.009 (S)	0.001 (S)
Mild	0.184 (NS)	0.045 (S)	0.026 (S)
Moderate	-	0.171 (NS)	0.184 (NS)
Severe	-	-	-

*P.O.Day: Post-operative day, NS: Non significant (P>0.05), S: Significant (P<0.05)

Table 5: Inter-group statistical comparison of serum potassium level (meq/l) in two study groups

Serum Potassium (mEq/L)	Group R Mean (±SD)	Group V Mean (±SD)	P-value
Sample I, Before Induction	4.23±0.58	4.25±0.54	0.858 (NS)
Sample II, after 5 min of Succinylcholine	4.44±0.58	4.45±0.53	0.928 (NS)

*NS: Non Significant (P>0.05)

potency.[28] The lack of potency of rocuronium compared with vecuronium is thought to be an important factor in determining the rapid onset of neuromuscular blockade produced by this drug. The large number of molecules administered when using a less potent nondepolarizing neuromuscular blocking drug results in a greater number of molecules being available to diffuse into the neuromuscular junction. Thus, a rapid onset of action is more likely to be achieved with rocuronium[29] and it could be effective against succinylcholine-induced fasciculations at intervals shorter than 3–5 min.[21]

In our study, we kept the waiting period of 60 s between pre-treatment with nondepolarizing muscle relaxant and succinylcholine administration. This is supported by Tsui et al.,[30] where they evaluated a rapid and time-saving regularization technique by using rocuronium 60 s before induction.

Findley and Spittal[16] also suggested that rocuronium, because of its rapid onset of action was effective in reducing myalgia when a short interval of one minute was allowed before induction. Abbas et al.,[31] and Abraham et al.,[18] also conducted their study with waiting period of 60 and 90 s respectively with rocuronium and control groups and rocuronium and vecuronium groups, respectively.

Motamed et al.,[21] conducted a study to assess the effects of rocuronium pre-treatment at 3 and 1.5 min before succinylcholine. They did not found any difference as regards to incidence of fasciculations and characteristics of succinylcholine blockade when time interval was reduced from 3 to 1.5 min. In our study, fasciculations were absent in 74% of the patients in the Rocuronium group as compared to 36% in the Vecuronium group (P=0.0001), whereas fine fasciculations (Grade 1) were observed in 24% of patients in the Rocuronium group as compared to 50% in Vecuronium (P=0.007). Only 2% of the patients had moderate fasciculations (Grade 2) in group R as compared to 14% in group V (P=0.028). None of the patients had vigorous fasciculations (Grade 3) in any group. Abraham et al.,[18] Kacha et al.,[19] Joshi et al.,[20] and Singh et al.,[23] all observed lower incidence of fasciculation with Rocuronium treated group.

In our study on 1st postoperative day, 94% and 86% of patients did not had any myalgia in group R and V respectively (P=0.184). Only 6% of patients in group R had mild myalgia as compared to 14% in group V, although it did not show statistical significance (P=0.184) this difference can be considered as clinically significant. None of the patients had moderate or severe myalgia in both groups.

On the 2nd postoperative day, a statistically significant difference (P=0.009) was observed in groups R and V where 64% and 38% of patients did not experience any myalgia. Further mild myalgia was observed in 34% and 54% of patients in group R and V, respectively (P=0.045). No statistically significant difference (P=0.171) between two study groups was observed as regard to moderate myalgia (2% and 8% in group R and group V, respectively).

On the 3rd postoperative day, 46% of patients in group R did not complain of myalgia as compared to 16% in group V (P=0.001), whereas mild myalgia was observed in 48% and 70% of the patients in group R and V respectively (P=0.026). Moderate myalgia was seen in 6% of patients in group R as compared to 14% in group V (P=0.184).

In this study, none of the patients experienced severe myalgia in both the groups on any postoperative day.

Depolarizing muscle relaxants such as succinylcholine bind both at pre-synaptic and post-synaptic sites to nicotinic acetylcholine receptors, but the pre-synaptic binding is thought to be associated with fasciculations.[32] If an NDMR is given before the succinylcholine, it will bind to pre-synaptic nicotinic neuronal acetylcholine receptors, thus blocking the binding of succinylcholine, resulting into reduced incidence of fasciculations.[33]

Similarly, Joshi et al.,[20] Singh et al.,[23] Farhat et al.,[34] Abbas et al.,[31] reported lesser incidence of myalgia with Rocuronium pretreated group patients as compared to Vecuronium. In contrast to our findings, Abraham et al.,[20] found statistically insignificant difference regarding postoperative myalgia on 1st and 3rd postoperative day (P>0.10).

The single dose administration of succinylcholine results in a rise of potassium concentration between 0.3 and 0.54mEq/L within 3–5 min and lasting up to 10–15 min. This rise is probably caused by potassium release from cells as a result of depolarization at the neuromuscular junction. Although this much rise has no serious effect in healthy individual but could lead to deleterious effects, especially in burn injury, massive trauma, severe intraabdominal infections, metabolic acidosis, spinal cord injury, polyneuropathy, myopathies, etc.

In our study, before induction of anesthesia (baseline) mean (±SD) serum potassium levels (mEq/L) were (4.23±0.58) and (4.25±0.54) in group R and V respectively (P=0.858). After 5 min of succinylcholine administration, a mild insignificant rise in serum potassium concentration (0.21±0.068) and (0.20±0.072) were observed in group R and V, respectively (P=0.928).

Abraham et al.,[20] Joshi et al.,[22] Farhat et al.,[24] also observed an insignificant rise in serum potassium after pre-treatment with Rocuronium and Vecuronium. In contrast to our finding, Singh et al.,[25] found that mean K^+ level was significantly more in the control group compared to the Rocuronium group, after 24 h of the postoperative period. (P=0.045).

With the exception of nausea in few patients (6% and 4% in group R and V, respectively), no other side-effects or complications were observed in both the study groups.

Limitations of the study

The present study has limitation of small sample size. Further studies are required to compare different doses and time intervals of administration of nondepolarizing muscle relaxants to assess effect of pretreatment on postsuccinylcholine fasciculations, serum pottasium levels and postoperative myalgia on a larger population.

CONCLUSION

We conclude that Rocuronium and Vecuronium, both are effective in attenuation of post succinylcholine fasciculations, rise in serum potassium and postoperative myalgia, but Rocuronium is more effective as compared to Vecuronium.

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Authors Contribution:
DK- Concept and design of the study, preparation of manuscript and revision of the manuscript; **ST-** Prepared first draft of manuscript, interpreted the results, reviewed the literature and revision of the manuscript; **RU-** Statistical analysis and interpretation

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