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Original Article

Comparative Evaluation of Sugammadex versus Neostigmine for Reversal of Neuromuscular Blockade in Patients Undergoing Cholecystectomy under General Anesthesia

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Abstract

Background and Aims: Muscle relaxation is the vital element of general anesthesia. It is attained using neuromuscular blocking agents (NMBAs). After surgery, full restoration of patient's muscle strength is essential to ensure safe post-operative recovery. The reversal of non-depolarizing NMBAs is achieved using acetylcholinesterase inhibitors or gamma-cyclodextrins. The present study was done to compare Sugammadex and neostigmine for the reversal of vecuronium-induced neuromuscular blockade in patients undergoing cholecystectomy under general anesthesia.

Materials and Methods: This prospective randomized double-blinded study was conducted in Guru Nanak Dev Hospital attached to Government Medical College, Amritsar, after taking written informed consent from patients in their vernacular language and approval from the Institutional Ethics Committee. This study was conducted on 60 patients, aged 18–60 years, American Society of Anesthesiologists Grade I and II, scheduled to undergo elective cholecystectomy under general anesthesia. The patients were randomly divided into two groups with 30 patients in each group. At the end of the surgery, when train-of-four (TOF) count reached 2, Group S patients received Sugammadex 2 mg/kg intravenously, and Group N patients received neostigmine 50 mcg/kg and glycopyrrolate 10 mcg/kg combination intravenously to reverse vecuronium induced neuromuscular blockade.

Results: The mean time from the study drug administration (at appearance of second twitch T2 after last dose of vecuronium) to tracheal extubation, that is, TOF ratio 0.9 was significantly faster in Sugammadex compared to neostigmine with 2.84 ± 0.592 min (mean ± standard deviation) in Group S and 14.168 ± 2.351 min in Group N. Furthermore, the mean time from study drug administration to operating room discharge ready was 8.92 ± 4.264 min in Group S, and it was 25.064 ± 10.208 min in Group N. Post-operative residual paralysis was not seen in any patient in both the groups.

Conclusion: Sugammadex is faster than neostigmine-glycopyrrolate combination in reversing vecuronium-induced neuromuscular blockade. Sugammadex is safe and well tolerated. The incidence of drug-related side effects (post-operative nausea vomiting, post-operative urinary retention) was slightly lower in the Sugammadex group as compared to neostigmine group (10% and 26.6%, respectively).

Key words: Neostigmine, Sugammadex, Vecuronium.

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INTRODUCTION

General anesthesia includes unconsciousness, amnesia, analgesia, muscle relaxation, and attenuation of autonomic responses to noxious stimulus. Muscle relaxation is the vital element of general anesthesia which is attained using neuromuscular blocking agents (NMBAs). An

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intermediately acting muscle relaxant, vecuronium is most widely used for muscle relaxation because it lacks histamine release and does not lead to ganglion and vagal nerve blockade.[1] Vecuronium is devoid of any significant cardiovascular effect. The length of neuromuscular blockade induced by vecuronium is therefore dependent primarily on hepatic function and, to less extent, on renal function.[2,3]

Neuromuscular monitoring performed using peripheral nerve stimulator, helps to guide intra-operative dosing of NMBA. It also helps to assess the adequacy of reversal and ensures that the patient recovers sufficiently from the residual effects of NMBAs (i.e. TOFR ≥ 0.90), thus assuring patient safety. Two or more twitches of the train-of-four (TOF) response should be detectable before reversal is given. The occurrence of residual blockade is significantly increased if the antagonism of neuromuscular blockade is omitted.[4] Residual neuromuscular blockade is often observed in patients after surgery in the recovery room, and it is related to significant morbidity.[5-8]

Pharmacological reversal of effects of non-depolarizing muscle relaxants is usually achieved using cholinesterase inhibitors. The increased acetylcholine will not only act at nicotinic receptors but also on muscarinic receptors resulting in muscarinic side effects. Due to their indirect mode of action, the reversal may be unpredictable and limited resulting in the patient being at higher risk of post-operative residual curarization. A synthetically modified form of gamma-cyclodextrin, Sugammadex selectively binds to muscle relaxant to form a complex which gets eliminated unchanged through the kidney. Sugammadex is used to reverse neuromuscular block induced by rocuronium/vecuronium in adults. Sugammadex helps in the predictable and faster reversal of any degree/depth of block due to its direct mode of action.[9]

MATERIALS AND METHODS

It was a prospective, randomized, double-blinded study conducted in Guru Nanak Dev Hospital attached to Government Medical College, Amritsar, after taking written informed consent from patients in their vernacular language and approval from the Institutional Ethics Committee. This study was conducted on 60 patients, aged 18–60 years, American Society of Anesthesiologists (ASA) Grade I and II, who were scheduled to undergo elective cholecystectomy under general anesthesia.

Sixty patients were randomly divided into two groups with 30 patients in each group. At the end of surgery, Group S patients received Sugammadex 2 mg/kg intravenously, and Group N patients received neostigmine 50 mcg/kg and glycopyrrolate 10 mcg/kg combination intravenously to reverse neuromuscular blockade.

The group allotment was decided using computer-generated random envelope method. The first anesthesiologist opened the envelope, prepared the study drug, and handed it to the second anesthesiologist, who was blinded to the study drug. He administered the study drug and monitored the patient.

A detailed pre-anesthesia checkup was done before the surgery. Details pertaining to patient's clinical history, general physical examination, and systemic examination were done and airway assessment was done. Patients were instructed to fast for 6 h for solids and 2 h for clear fluids before surgery.

On the day of surgery, the patient was shifted to operation theatre, and multiparameter monitor was applied, that is, non-invasive blood pressure, pulse oximetry, electrocardiogram, neuromuscular monitoring, and end-tidal carbon dioxide before induction of anesthesia. Intravenous (I.V) cannula 20 gauge was inserted and injection midazolam 0.02–0.03 mg/kg and injection butorphanol 0.015–0.02 mg/kg were given i.v. to all patients. Patients were pre-oxygenated through face mask for 3 min. General anesthesia was induced using propofol 1.5–2 mg/kg, bolus dose of vecuronium 0.08–0.1 mg/kg given, i.v., intermittent positive pressure ventilation with oxygen for 2–3 min. Patient's trachea was intubated with endotracheal tube of required size, cuff was inflated, bilateral air entry was checked, tube was fixed and secured, and confirmation of the tube was done by capnography.

Neuromuscular monitoring was done by stimulating the radial nerve and evaluating the contraction of the adductor pollicis muscle. Neuromuscular monitoring was started after induction of anesthesia but before the administration of vecuronium using TOF watch. Neuromuscular monitoring using a peripheral nerve stimulator was used to guide intraoperative dosing of NMBA. It also helped to assess adequacy of reversal, that is, it ensured that the patient recovered adequately from residual effects of NMBD (i.e. TOFR ≥ 0.90), thus guaranteeing patient safety. TOF ratio of 0.9 is considered to be a safe value for deciding upon extubation. At least two twitches of the TOF response should be detectable before the reversal is given.

General anesthesia was maintained with 50% oxygen in 50% nitrous oxide, isoflurane 1.2 minimum alveolar concentration, and injection vecuronium 0.01–0.015 mg/kg maintenance. Injection ondansetron 4 mg i.v. was administered 15 min before end of surgery.

For analgesia, paracetamol infusion 10–15 mg/kg was given. On completion of the surgery, with the patient properly anesthetized, posterior pharynx was carefully suctioned using the blunt suction catheter. All anesthetic gases were stopped, and inspiratory oxygen concentration was increased to 100% 5 min before extubation.

At the end of the surgery, when the response reached a TOF score of 2, patients in Group S received Sugammadex (2 mg/kg) and Group N received neostigmine (50 mcg/kg) and glycopyrrolate (10 mcg/kg). The neuromuscular functioning was recorded and time required to achieve 90% of TOF was measured. Extubation was done on the return of spontaneous ventilation when the TOF ratio reached ≥0.9. In the recovery room, patient received oxygen through simple oxygen mask and monitoring was done.

Statistical Analysis

The sample size was calculated keeping in view at most 5% risk, with minimum 85% power and 5% significance level (significant at 95% confidence interval [CI]). Data were recorded in a Microsoft Excel spread sheet and analyzed using Statistical Package for the IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp., Chicago.

Continuous data were presented as mean with standard deviation (SD). Categorical data were expressed as percentages. Numerical variables were normally distributed and were compared using Chi-square test for non-parametric data and "t" test for parametric data. The p value was then determined to evaluate the level of significance. This study was conducted on 60 patients who were randomly divided into two groups, with 30 patients in each group. The data from the present study were systematically collected, compiled, and statistically analyzed to draw relevant conclusions.

After consulting with statisticians and monitoring the parameters of the study, that is, time from the last dose of vecuronium to recovery of TOF ratio of 0.9, time from study drug administration to tracheal extubation, time from the study drug administration to operating room discharge ready, side effects of both the drugs, etc. and to make the power of study more than 85%. The above-mentioned parameters and patient's characteristics were compared using appropriate statistical tests. The results were analyzed and compared to previous studies.

RESULTS

A total of 60 patients were studied and analyzed. The demographic parameters such as age, sex, weight, ASA grade, and mean duration of surgery were comparable in both groups [Table 1].

The mean time from the last maintenance dose of vecuronium to recovery of TOF ratio of 0.9 was 18.920 ± 2.033 min in Group S and 28.354 ± 3.280 min in Group N which was found to be significant ($P = 0.001$) [Figure 1].

The mean time from study drug administration (at reappearance of second twitch T2 after last dose of vecuronium) to tracheal extubation, that is, TOF ratio 0.9 was significantly faster with Sugammadex compared with neostigmine with 2.84 ± 0.592 min (mean ± SD) in Group S and 14.168 ± 2.351 min in group N with ($P = 0.001$) [Table 2].

The mean time from study drug administration to operating room discharge ready was 8.92 ± 4.264 min in Group S, and it was 25.064 ± 10.208 min in Group N, which was significant ($P = 0.001$) [Figure 2].

Table 1: Demographic parameters

Parameter	Group S	Group N	*P*-value
Mean age (years)	37.830±10.120	37.370±10.540	0.430
Sex (number)			
Male	3	5	0.447
Female	27	25	
Weight (kg)	65.650±5.820	63.390±9.230	0.130
ASA grade			
I	21	23	0.559
II	9	7	

NS: Non-significant ($P>0.05$); S: Significant ($P<0.05$); HS: Highly significant ($P<0.001$)

Table 2: Mean time from study drug administration to tracheal extubation (min)

Study group	Time from study drug administration (at TOF score of 2) to tracheal extubation at TOF ratio of 0.9 (min)	
	Mean	Standard deviation
Group S	2.840	0.592
Group N	14.168	2.351
t-value	−23.821	
P-value	0.001	

NS: Non-significant ($P>0.05$); S: Significant ($P<0.05$); HS: Highly significant ($P<0.001$)

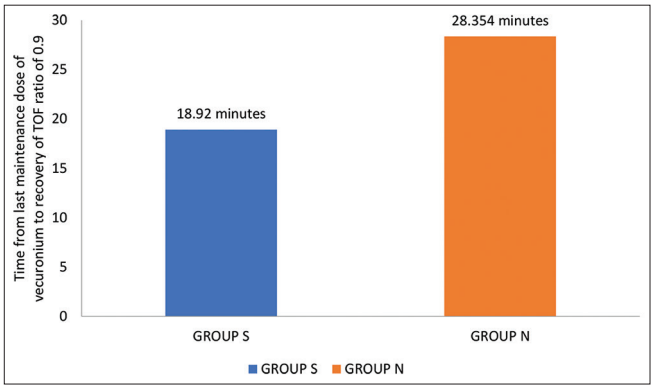

Figure 1: Time from last maintenance dose of vecuronium to recovery of train-of-four ratio of 0.9 (min)

In Group S, 2 out of 30 patients had post-operative nausea/vomiting (PONV) and 1 out of 30 patients had post-operative urinary retention (POUR). In Group N, five out of 30 patients had PONV and 3 out of 30 patients had POUR. Post-operative residual paralysis (PORP) was not seen in any patient in both the groups. The difference in both the groups was non-significant ($P = 0.992$). No serious drug-related adverse event occurred in any group [Figure 3].

DISCUSSION

The study was carried out to compare the safety and efficacy of Sugammadex with neostigmine for reversing vecuronium-induced neuromuscular blockade and to study the safety profile of Sugammadex.

In our study, the mean time from last maintenance dose of vecuronium to the recovery of TOF ratio to 0.9 was 18.920 ± 2.033 min in Group S and 28.354 ± 3.280 min in Group N which was found to be significant

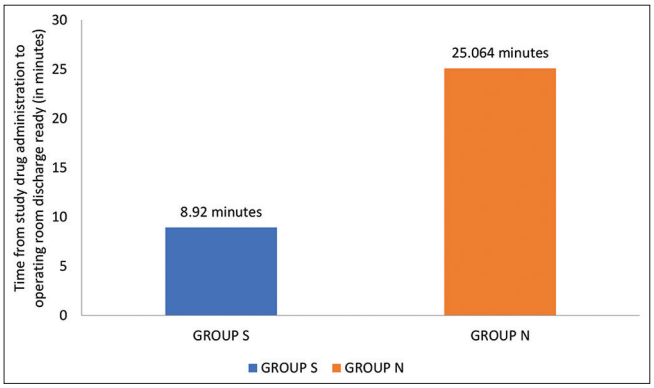

Figure 2: Time from study drug administration to operating room discharge ready (min)

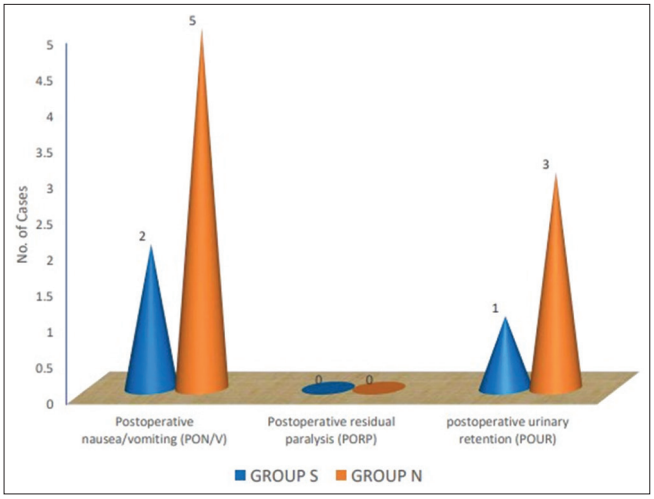

Figure 3: Side effects if any (post-operative nausea/vomiting, post-operative residual paralysis, post-operative urinary retention)

($P = 0.001$). Sugammadex is significantly faster in reversing neuromuscular blockade attributable to its novel mechanism of action by encapsulating the NMBA, which is then unavailable to bind to the acetylcholine receptors at the neuromuscular junction.

In the present study, the mean time from study drug administration (at reappearance of second twitch T2 after last dose of vecuronium) to tracheal extubation, that is, TOF ratio 0.9 was significantly faster in Sugammadex compared to neostigmine. It was 2.84 ± 0.592 min (mean ± SD) in Group S and 14.168 ± 2.351 min in Group N with ($P = 0.001$).

A similar study was conducted by Khuenl-Brady *et al*.[10] in 2010, on Sugammadex providing faster reversal of neuromuscular blockade induced by vecuronium and compared it with neostigmine. They concluded that the geometric mean time, that is, time from the start of the study drug administration to the recovery of TOF ratio to 0.9 was significantly faster in Sugammadex, that is, 2.7 min [95% CI]: 2.2–3.3 min) when compared to neostigmine, that is, 17.9 min [95% CI: 13.1–24.3 min], ($P < 0.0001$).

Similarly, a meta-analysis was done by Hristovska *et al*.[9] in 2018 using 10 studies to study the comparative safety and efficacy of neostigmine and Sugammadex for reversing neuromuscular block in adults. They concluded that the time for neuromuscular blockade reversal from second twitch to TOF ratio >0.9 was 12.9 min with neostigmine 0.05 mg/kg and 2.0 min using Sugammadex 2 mg/kg.

In our study, after using vecuronium as NMBA, the time from study drug administration to operating room discharge ready was 8.92 ± 4.264 min in Group S, and it was 25.064 ± 10.208 min in Group N, which was significant ($P = 0.001$).

Similar findings were observed by Putz *et al*.[11] in 2016 who conducted a study to assess operating room discharge after reversing deep neuromuscular block using Sugammadex compared to shallow block reversed with neostigmine. They concluded that time from the study drug administration to operating room discharge was shorter in Group S, that is, 9.15 ± 4.28 min when compared to Group N, that is, 13.87 ± 11.43 min ($P = 0.005$).

Our results were also comparable to a study conducted by Brueckmann *et al*.[12] in 2015 on the effects of Sugammadex on the incidence of post-operative residual neuromuscular blockade using rocuronium as NMBA. They concluded that the geometric mean time (in minutes) from the study drug administration to operating room discharge ready in

Sugammadex group was 14.7 min and in usual care patients (neostigmine/glycopyrrolate) was 18.6 min.

In our study, the prevalence of adverse events related to the drug (PONV, POUR, PORP) was slightly more in neostigmine group as compared to Sugammadex group (26.6% and 10% respectively). Our results were comparable to the study done by Khuenl-Brady *et al*.[10] in 2010 on Sugammadex providing faster reversal of neuromuscular block induced by vecuronium when compared to neostigmine. It was concluded that the profile and incidence of adverse events related to the drug were generally lower and almost similar in both Sugammadex and neostigmine groups and no serious adverse event was reported. The drug-related adverse events were slightly more in neostigmine group like dry mouth, increased/decreased heart rate as compared to Sugammadex group (22.2% and 14.6%, respectively).

Limitations

- The major limitation of our study was the small sample size but it had significantly important results, so future studies should be undertaken with a large population size.
- Sugammadex, being more costly than Neostigmine is another factor limiting its use as a reversal agent in in a developing country like India.

CONCLUSION

Sugammadex is faster than neostigmine-glycopyrrolate combination in reversing the vecuronium-induced neuromuscular blockade. Sugammadex is safe and well tolerated. Although statistically insignificant, the incidence of drug-related side effects (PONV, POUR) was slightly lower in the Sugammadex group when compared to neostigmine group. In both the groups, PORP was not observed in any patient. Both the groups were comparable with respect to hemodynamic parameters like BP, PR, and SPO_2 with the difference being statistically non-significant. No drug-related serious adverse event occurred in any group.

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