ASSESSMENT OF DIFFERENT DOSES OF NEOSTIGMINE IN REVERSING CISATRACURIUM INDUCED NEUROMUSCULAR BLOCK BY USING NEUROMUSCULAR MONITOR: A PROSPECTIVE, DOUBLE-BLIND RANDOMIZED TRIAL

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ABSTRACT

Objective: This study aimed to evaluate the effectiveness of different reversal strategies with neostigmine in cisatracurium-induced neuromuscular blockade by, focusing on recovery times, incidence of residual blockade, and patient safety profile.

Methods: A prospective, randomized, double-blind trial was conducted involving six groups of patients (n=30 each) receiving different dosages of neostigmine at different TOF ratios. Neuromuscular function recovery, residual blockade incidence, and safety were assessed using various measurements. Statistical analysis included ANOVA, Chi-square tests, and post-hoc analyses.

Results: The study found that recovery times varied based on neostigmine dosages and train-of-four (TOF) ratios at the time of administration. The study groups exhibited varying mean times to achieve TOF ratios of 0.9 and 1.0 after neostigmine administration. The incidence of post-extubation TOF ratios below 0.9 showed no substantial variation among the groups. The overall incidence of adverse effects was low, with no significant differences observed among the study groups.

Conclusion: The study concludes that 30 mcg/kg administered at TOF ratio 0.6 may be the most effective dosage of neostigmine for rapid and sufficient recovery from shallow neuromuscular blockade at TOF ratio 0.4 or 0.6, with the fewest adverse effects. 20 mcg/kg is the lowest dose that can be used to successfully restore shallow neuromuscular block, albeit it does take longer time.

Keywords: Neuromuscular block, Neostigmine, Cisatracurium, Residual paralysis, Neuromuscular monitoring, Safety profile, Anesthesia, TOF ratio

INTRODUCTION

Neuromuscular blocking (NMB) drugs enable tracheal intubation, mechanical ventilation, and muscle relaxation under general anesthesia. However, improper withdrawal from these drugs can lead to negative outcomes, such as respiratory problems and muscle weakness. Postoperative paralysis caused by inadequate NMB drug reversal can result in severe respiratory complications, including reduced pulmonary function, upper airway blockage, and aspiration risk. A train-of-four (TOF) ratio below 0.7 signifies residual NMB, but recent research suggests that even ratios of 0.7 to 0.9 pose risks. Neostigmine is a common reversal agent, but factors like degree of block at the time of administration and concurrent anesthesia impacts its effectiveness [1].

The neuromuscular junction (NMJ) is where nerve impulses translate to muscle contractions. It consists of presynaptic terminals, synaptic cleft, acetylcholine receptors, and contractile apparatus. Acetylcholine, stored in vesicles, aids in muscle contraction [2]. Neuromuscular transmission involves acetylcholine release from vesicles, binding to receptors, depolarization of muscle endplates, calcium release, and actin-myosin cross-linking. Acetylcholinesterase degrades acetylcholine, allowing muscle relaxation. Neuromuscular blockers interfere with this process, leading to paralysis [3].

Neostigmine, an anticholinesterase drug, reverses neuromuscular blockade by inhibiting acetylcholinesterase. It forms a reversible carbamyl ester complex, enhancing acetylcholine availability. Neostigmine's effectiveness depends on factors like dosage, timing, and individual responses.

Cisatracurium, a nondepolarizing skeletal muscle relaxant, have moderate onset and duration of action, undergoing plasma breakdown without affecting the liver or kidneys. It is used in conjunction with anesthesia and should be stored and administered correctly to maintain efficacy [4].

Neuromuscular monitoring techniques like single twitch, double burst, TOF, tetanic stimulation, and PTC aid in evaluating neuromuscular function recovery after use of NM-blocking drugs. They contribute to effective anesthesia its recovery and minimizes risks during surgery and recovery [5].

MATERIALS AND METHODS

This was a prospective, randomised, interventional, double-blind experiment. The research was carried out after approval from the institutional ethics committee. With the informed written consent of all the participants, the study was done at the anaesthesia department of SMS Medical College Jaipur.

After approval of synopsis from DRC of RUHS, Jaipur and CTRI registration (registration number CTRI/2020/08/027270 on dated 20.08.2020) the study was started and continued till completion of the sample size (In the year 2020-21).

Sample size

At three dosages of neostigmine (20, 30 or 40 micro gm/kg), a sample size of 30 participants in each group was determined to be sufficient at a 95% confidence level and 80% power to verify the minimum predicted difference of 2.2 (2.13) minutes in attaining full reversal of neuromuscular block [6].

From all 180 eligible patients, six groups of 30 patients each were created at random. Patients in Groups A, B, and C (n=30) got neostigmine (20, 30, and 40 micro g/kg, respectively) with glycopyrrolate at 0.4 TOF ratio.

Patients in Groups E, F and G (n=30) received neostigmine (20, 30 and 40 micro g/kg, respectively) with glycopyrrolate at a TOF ratio of 0.6.

The anaesthesiologist who gave anaesthesia to patients would be different from the anaesthesiologist who collected and analysed data to confer the blinding.

The method of randomisation was computerised by using a sequentially numbered sealed envelope approach.

Eligibility criterion

Patient of either sex, with age 20-40 y, weight 40-70 kgs and belonging to ASA I or II class posted for surgery(duration lasting from 60-150 min) requiring general anesthesia were included in study.

Patients with a history of any known neuromuscular disease/cardiac/respiratory/hepatic/renal disease were excluded. Patients using drugs that affect NM blockage, such as gentamycin, CCB, phenytoin, steroids, frusemide, magnesium, lithium, procainamide, etc. were also excluded.

On the day before surgery, every patient informed about the anaesthetic method and postoperative course. Every patient underwent a complete pre-anesthetic examination, including required investigations.

Following thorough explanations of the research protocol,all patients had the option to withdraw from the research at any time.

After confirming the patient's identity and pre-anesthesia fasting of six hours, all patients were anesthetised and intubated by similar standard protocol.

Cisatracurium was used as NM blocking agent under the standard monitoring along with TOF monitoring.

After completion of surgery every patient was given neostigmine along with glycopyrolate in dose according to group allocated.

TOF monitoring was done regularly during all the period.

RESULTS

Both the groups were comparable in relation to their baseline characteristics like age, gender, BMI (body mass index) and ASA grading (table 1). The total cumulative dose of cisatracurium given and the total duration of surgery were statistically non-significant among the study groups.

Table 2 displays the time taken to achieve Train of Four (TOF) ratios of 0.9 and 1.0 after neostigmine administration. Post-hoc analysis of variants using ANOVA test was conducted. Each group showed varying mean times for achieving the desired TOF ratios. The time it took to attain the TOF 1.0 target in our study for 30 mcg/kg at TOF 0.6 (Group E), 40 mcg/kg at TOF 0.4 (Group C), and 40 mcg/kg at TOF 0.6 (Group F) was statistically non-significant (p 0.05). All these dosages were able to completely reverse 100% of instances in 6.5 min or less. All other groups have a significantly high time for complete reversal.

Table 1: Demographic data, ASA class, total duration of surgery, total dose of cisatracurium wise distribution of patients

Variables		Group A	Group B	Group C	Group D	Group E	Group F	"p-value"
Age (mean±sd)		34.43±5.12	33.10±5.93	33.17±5.28	35.33±3.81	35.33±3.81	35.13±4.29	0.821
Gender	Male	16±53.33	17±56.66	17±56.66	12±40.00	13±43.33	14±46.66	0.830
	Female	14±46.66	13±43.33	13±43.33	18±60.0	17±56.6	16±53.3	0.830
BMI		24.41±1.64	23.90±2.10	23.96±1.01	24.22±1.86	24.73±1.55	24.44±1.22	0.339
ASA	Grade 1	16±53.3	18±60.0	16±53.3	16±53.3	17±56.6	16±53.3	1.000
	Grade 2	14±46.66	12±40	14±46.66	14±46.66	13±43.3	14±46.66	1.000
Total duration of surgery		93.83±25.18	98.50±25.67	93.17±28.48	96.50±27.02	90.50±21.87	96.	0.883
Total dose of cisatracurium		12.59±1.45	12.94±1.29	12.77±1.26	12.87±1.32	12.45±1.06	12.65±1.51	0.72

Table 2: Time to achieve TOF ratio 0.9 and TOF ratio 1.0 among various study groups(In minutes)

	Group A		Group B		Group C		Group D		Group E		Group F	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Time to achieve TOF ratio 0.9 after giving neostigmine	7.14	0.65	6.06	0.53	5.53	0.26	6.73	0.44	5.59	0.51	5.38	0.56
Time to achieve TOF ratio 1.0 after giving neostigmine	8.20	0.56	6.52	0.52	6.28	0.25	7.72	0.43	6.09	0.51	6.17	0.53

Table 3: Adverse incidents in percentage

	Group A	Group B	Group C	Group D	Group E	Group F	Total
Nil	86.67	90	90.00	90.00	90.00	90.00	89.5
N and V	6.67	3.33	6.67	0.00	3.33	10.00	5
Difficulty in swallowing	6.67	6.67	3.33	10.00	6.67	0.00	5.5

Chi-square = 7.407; p=0.687(NS)

Table 3 provides insights into adverse incidents among the study groups. The Chi-square test yielded a non-significant p value of 0.687, implying no significant disparity in the incidence of adverse effects. Although the overall incidence was not statistically significant, a small percentage reported difficulties in swallowing (5.5%) and nausea/vomiting (5%) across the groups.

DISCUSSION

The present study provides valuable insights into the effective management of residual neuromuscular blockade following general anesthesia using neostigmine as a reversal agent. Our investigation focused on the recovery times and safety profile associated with varying doses and ratios of neostigmine administration. The findings from our study shed light on the optimal dose and time of administration of neuromuscular blockinduced by cisatracurium, as well as the safety considerations surrounding neostigmine administration [6].

The consistent distribution of demographic data (table 1) across all study groups minimizes the potential impact of body composition on the study outcomes. This uniformity ensures that observed differences in recovery times and effectiveness of neostigmine are less likely to be influenced by variations in metabolism or distribution of the drug due to differences in BMI.

The recovery times presented in table 2 demonstrate a clear relationship between neostigmine dosages, TOF ratios, and the speed of neuromuscular blockade reversal [7]. Notably, higher dosages of neostigmine administered at higher TOF ratios lead to faster recovery, underscoring the importance of tailored dosing strategies based on the depth of neuromuscular blockade. This aligns with prior studies that suggest neostigmine's efficacy is dependent on its dosage and the degree of neuromuscular blockade present at the time of administration [8].

Our findings corroborate the notion that all the neostigmine doses of 20, 30 and 40 mcg/kg are effective in reversing shallow neuromuscular blockade (TOF ratios 0.4 and 0.6) to TOF ratio 1.0. The variations in recovery times among different dose and TOF ratios are consistent with the established pharmacokinetics of neostigmine. Moreover, the prompt reversal achieved with higher dosages is consistent with studies suggesting that higher doses can overcome neostigmine's ceiling effect and accelerate recovery from neuromuscular blockade [9].

The safety profile of neostigmine is a critical consideration in its clinical application. Table 3 shows the adverse incidents, including nausea, vomiting, and swallowing difficulties, were generally infrequent and not significantly associated with neostigmine use. This aligns with prior research suggesting that neostigmine is well-tolerated and associated with minimal adverse effects when administered within appropriate dosages [10].

While our study provides valuable insights, certain limitations should be acknowledged. The study population was limited to a specific demographic, and the study duration might not have captured long-term recovery trends. Additionally, the study's focus on cisatracurium-induced blockade might limit the generalizability to other neuromuscular blockers [11].

CONCLUSION

Our study underscores the effectiveness and safety of neostigmine administration for reversing neuromuscular block induced by cisatracurium. Tailored dosing strategies based on neostigmine dose and timing of its administration on the basis of TOF ratios can lead to prompt recovery of neuromuscular function.

The study concludes that 30 mcg/kg administered at TOF ratio 0.6 may be the most effective dose of neostigmine for rapid and sufficient recovery from shallow neuromuscular blockade at TOF ratio 0.4 or 0.6, with the fewest adverse effects. 20 mcg/kg is the lowest dose that can be used to successfully restore shallow neuromuscular block, albeit it does take longer time.

The low incidence of adverse events further supports the clinical utility of neostigmine in anesthesia practice.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

Declared none

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