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A COMPARATIVE STUDY OF ATROPINE AND GLYCOPYRROLATE IN COMBINATION WITH NEOSTIGMINE FOR REVERSAL OF NEUROMUSCULAR BLOCKADE

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Abstract

This study was conducted to compare the haemodynamic effects and clinical effectiveness of Atropine versus Glycopyrrolate along with Neostigmine for reversing non-depolarizing neuromuscular blocking agents (NMBAs) in patients with elective surgery under general anaesthetic. There were 110 adult patients of ASA physical status I-II who were enrolled and divided into two groups: Group A (Atropine + Neostigmine, n=60) and Group B (Glycopyrrolate + Neostigmine, n=50). Data was obtained using a structured Performa and was analysed using SPSS version 25.0. The 2 groups had no statistically significant difference in baseline demographic and physiological parameters such as age, heart rate and ASA classification ($p>0.05$) and therefore successful group allocation was achieved. There was effective control of secretions and complete prevention of bradycardia in both groups with no bradycardia occurring in either group. There was a highly significant difference between the two groups with 40 patients (66.7%) having tachycardia in the Atropine + Neostigmine group and none (0%) in the Glycopyrrolate + Neostigmine group (p 0.001, $\chi^2 = 52.381$, $df = 1$). These results show that both agents prevent bradycardia equally well and control secretions equally well, but that Glycopyrrolate has a markedly more favourable cardiovascular safety profile, with no risk of tachycardia. Use of Glycopyrrolate and Neostigmine is shown to be a more hemodynamically stable alternative for the reversal of neuromuscular blockade than the use of Atropine and should be preferred in clinical anesthetic practice, especially in patients at cardiovascular risk.

INTRODUCTION

The neuromuscular blocking agents (NMBAs) play a critical role in anesthesia in muscle relaxation during surgical procedures. They are either non-depolarizing or depolarizing agents and with depolarizing agents that activate the receptors of acetylcholine and non-depolarizing agents blocking them. NMBAs are usually given intravenously, intramuscularly, or intraosseous, and they are dosed according to the characteristics of the patients[1]. Neuromuscular blocking agents (NMBAs) are commonly used in contemporary anesthetic treatment used to induce skeletal muscle relaxation in surgery, ease endotracheal intubation, and provide optimal operating conditions. These medications are vital

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in general anesthesia as they enhance the exposure to the surgery, allow regulated respiration, and prevent mobility of patients during the procedure being conducted. The use of neuromuscular blocking drugs can cause residual neuromuscular block after surgery, despite its therapeutic benefits. A few surgical issues, such as airway obstruction, respiratory insufficiency, hypoxia, risk of aspiration, and delayed recovery in the post-anesthesia care unit, are associated with residual blockage2. On a worldwide scale, residual neuromuscular blockade continues to be a major clinical problem. In case of neuromuscular blocking medications, according to studies, when they are given after surgery, a significant percentage of patients have an incomplete recovery of neuromuscular function. This syndrome, also known as postoperative residual, curarizes, might enhance morbidity during post-operative period by making respiratory systems and airways more vulnerable reflexes[3]. Due to this, it is safe and effective to reverse neuromuscular blockade, which is considered a very important part of anesthesia management. Most used anticholinesterase drugs are used to reverse neuromuscular blockage is neostigmine. Neostigmine increases by inhibiting the enzyme acetylcholinesterase in the quantity of acetylcholine in the neuromuscular junction. Competition with non-activating nicotinic receptors, elevating acetylcholine, by depolarizing neuromuscular blocking drugs availability enhances muscle strength and neuromuscular transmission of significance is restored[4]. Neostigmine activates the acetylcholine-receptors at muscarinic receptors of various organs, despite its common use and usually successful application. Bradycardia, bronchoconstriction, increased salivation, increased bronchial secretion, increased gastrointestinal motility are some of the adverse effects of neostigmine activation of muscarinic receptors[5]. Poor control of these muscarinic actions in the reversal stage can be life threatening, e.g cardiovascular and respiratory instability. Neostigmine is thus commonly used in conjunction with anticholinergic drugs to counteract these unfavorable parasympathetic effects. The most used anticholinergic

drugs are atropine and glycopyrrolate in neuromuscular block reversal. The tertiary amine anticholinergic drug atropine has been used for many years in anesthetic practices. It efficiently avoids bradycardia induced by neostigmine and is fast-acting. Atropine, on the other hand, easily passes across the blood brain barrier and could result in side effects of the central nervous system such as agitation, disorientation, or restlessness. Moreover, atropine can increase the heart rate rapidly, which in turn can be dangerous. There are instances that can lead to tachycardia and hemodynamic instability[6]. However, the quaternary ammonium molecule glycopyrrolate does not enter the blood–brain barrier. Glycopyrrolate does not impact much on the central nervous system. Although it is slightly slower than atropine and successfully blocks muscarinic receptors and is associated with longer lasting cardiovascular responses. Moreover, glycopyrrolate is effective in reducing bronchial and salivary secretions, which can possibly improve airway management during anesthesia and recuperation[7]. The use of atropine and glycopyrrolate in conjunction with neostigmine to reverse neuromuscular inhibition has been compared in a few clinical trials. Previous studies showed that, when compared to atropine, glycopyrrolate provides similar protection against induced bradycardia with a lesser increase in heart rate[8]. According to additional research, glycopyrrolate may result in more stable cardiovascular measures, such as mean arterial pressure and heart rate particularly in elderly surgery patients[9,17]. The selection of the right reversal drugs is essential in improving the outcome of surgery, and residual neuromuscular blockade continues to be a worldwide patient's safety concern various rates of residual neuromuscular blockade postoperative have been reported in international studies, with the importance of proper monitoring and pharmacological reversal techniques[10].

METHODOLOGY

The purpose of this randomized comparative

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study is to assess and compare the clinical effectiveness and safety of atropine and glycopyrrolate given with neostigmine for reversal of neuromuscular blockade at the end of general anesthesia. The study is conducted according to the ethical standards in place and informed written consent was obtained from all the patients included in the study before the beginning of the study. The study was conducted at PHQ Teaching Hospitals Gilgit over a period of march 2026 to July 2026. A total of 110 were enrolled and subsequent divide in two treatment groups:

- Group A (n=60) Atropine + Neostigmine.
- Group B (n=50) Glycopyrrolate + Neostigmine.

Patients aged 18–90 years, Patients undergo surgery under general anesthesia, Patients with ASA physical status I and II, Schedule for Elective surgery under General Anesthesia, Required Neuromuscular blockade reversal at the end of surgery were included in this study and Patients with known cardiovascular disease, Patients undergoing procedures under regional or local anesthesia, Patients with respiratory disorder (e.g. asthma, COPD), Pregnant or lactating female, Patient with ASA physical status iii and iv were excluded in this study. Patients were randomly allocated into one of the treatments according to reversal drugs they received using a sealed envelop method. The group assessment is performed by anesthesiologists who had not involved in data collection to minimize observer bias. A uniform anesthetic technique is used for all participants. All patients were kept on NPO (nil per oral) for at least 6-8 hours prior to surgery. Intraoperative monitoring is done with electrocardiography (ECG), pulse oximeter (SpO2) and non-invasive blood pressure (NIBP) monitoring.

Intravenous Propofol (2mg/kg) and Fentanyl (2mcg/kg) were used to induced anesthesia. Atracurium (0.5mg/kg) were used to induce neuromuscular blockade and Isoflurane was used with in combination with oxygen and air to maintain anesthesia. At the end of surgery, reversal of neuromuscular blockade is started once the train-of-four (TOF) ration demonstrated a minimum of two twitches. The respective drugs combination was administrated as follow:

- Group A: Neostigmine 0.05mg/kg + Atropine 0.02mg/kg intravenously.
- Group B: Neostigmine 0.05mg/kg + Glycopyrrolate 0.01mg/kg intravenously.

In both groups, the combination is delivered slowly over period of 60 seconds to ensure uniformity and consistency in administration across all patients. Data will be collected through a slightly modified predesigned Performa. Patients undergoing general anesthesia will be monitored perioperatively, to record baseline of heart and intraoperative for hemodynamic changes. Relevant data will be recorded, including demographic details, study drugs administration, and recovery time will be recorded. All collected data were entered and analysed using SPSS version 25.0 and M.S Excel 2024. Statistics, Chi Square test, Independent Sample T- test and crosstab is used.

RESULTS

Table 1: Comprehensive Summary of Statistical Results

Variable	Atropine Group (n=60)	Glycopyrrolate Group (n=50)	Statistical Test	Test Value	p-value	Result
Tachycardia Yes n (%)	40 (66.7%)	0 (0.0%)	Chi-Square	$\chi^2 = 52.381$	0.001	
ASA Classification	I=29, II=31	I=31, II=19	Chi-Square	$\chi^2 = 2.055$	0.152	NS
Bradycardia Yes n (%)	0 (0.0%)	0 (0.0%)	N/A	N/A	N/A	

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The incidences of tachycardia, bradycardia, and ASA classification between the Atropine + Neostigmine group and Glycopyrrolate + Neostigmine group are compared in Table 1. There was a high association between the use of atropine and incidence of tachycardia, as a significantly higher proportion of patients in the Atropine group developed this effect, compared with the Glycopyrrolate group (66.7% vs. 0.0%, χ^2 = 52.381, p = 0.001). There were no findings of bradycardia in either group. However, there was no statistically significant difference in ASA classification between the two groups (χ^2 = 2.055, p = 0.152), indicating that there was no significant difference in baseline physical status between these groups.

In summary, Table 1 shows that both drugs were used in similar patient populations, but Glycopyrrolate was significantly less likely to affect the heart rate and other cardiovascular side effects, and more hemodynamically stable in clinical practice.

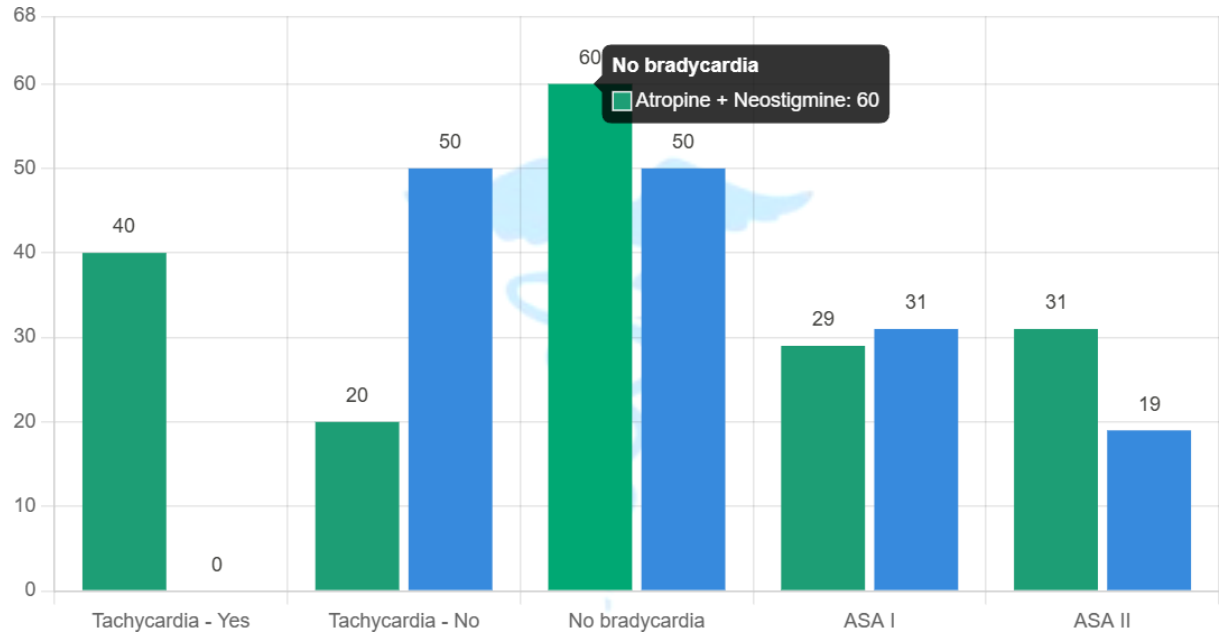

Figure 1: Comprehensive Comparison Between Anesthetic Reversal Regimens

This grouped bar chart provides a detailed comparison of two anesthetic reversal regimens (Atropine + Neostigmine and Glycopyrrolate + Neostigmine) in 5 clinical parameters in one chart. Tachycardia (Yes): 40 patients in Atropine + Neostigmine group had Tachycardia, in Glycopyrrolate + Neostigmine group, no patients had Tachycardia (0). This is the largest difference between the two groups. No patient in the Atropine group and all 50 patients in the Glycopyrrolate group had no tachycardia. No bradycardia in either group: In the Atropine group, 60 patients had no cases of bradycardia and in the Glycopyrrolate group, 50 patients had no case of bradycardia. There was no difference between both groups in this parameter.

There were 29 patients in the Atropine group who were ASA classed as I, while 31 patients were ASA classed as I in the Glycopyrrolate group. ASA II: 31 patients were rated ASA II in the Atropine group and 19 patients were rated ASA II in the Glycopyrrolate group.

The most striking results is that Atropine + Neostigmine had a much higher incidence of tachycardia (40 cases), whilst Glycopyrrolate + Neostigmine seemed to be significantly more cardiac-stable with none of these side effects. Neither regimen had any risk of bradycardia.

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There are also a number of differences in the ASA distribution; the more favourable outcomes of the Glycopyrrolate group may be accounted for by the fact that there were a higher proportion of healthy (ASA I) patients. The data collectively indicates that Glycopyrrolate is the safer of the two when it comes to the prevention of tachycardia and other cardiovascular effects.

Definitive Assessment

Excluding those who were reversed following general anesthesia, 110 patients were reversed for the primary reason of neuromuscular blockade reversal, in which neostigmine was used with Atropine or Glycopyrrolate. The most important adverse effect was tachycardia: present in 40 patients (66.7%) in the Atropine group, not observed in the Glycopyrrolate group, with a highly statistically significant difference (p 0.001). The ASA classification was similar for both groups, with a small number of ASA Class II patients in the Atropine group, but without statistical significance (p = 0.152). Bradycardia occurred in none of either group, suggesting both drugs provided good anticholinergic cover**.**

Train of Four (TOF) Monitoring

This is the gold standard method for confirming neuromuscular reversal. A peripheral nerve stimulator delivers four successive electrical stimuli and the muscle response is measured. A TOF ratio of 0.9 or above is considered the definitive confirmation that neuromuscular blockade has been completely reversed.

Clinical sign of Adequate Reversal

These consist of being able to lift the head for 5 seconds, adequate grip strength of the hands, tongue depressor test, and return of sufficient tidal volume all of which clinically indicate full restoration of muscle power.

Hemodynamic Monitoring

Changes in heart rate such as tachycardia and bradycardia are objectively measured. As seen in table 1 of your study, the percentage of patients with tachycardia in the Atropine group was 66.7% vs 0% in the Glycopyrrolate group, which is clearly helpful to demonstrate the cardiovascular safety profile of each drug.

Respiratory Assessment

SpO2, respiratory rate and breathing pattern are assessed to ensure the patient can breathe freely and effectively independently the best clinical evidence of successful neuromuscular reversal.

DISCUSSION

This was a randomized comparative study for the evaluation and comparison of the hemodynamic effects of Atropine and Glycopyrrolate given in combination with Neostigmine for reversal of neuromuscular blockade in 110 adult patients who were undergoing elective surgery under general anesthesia. Results offer valuable clinical information concerning the cardiovascular safety of each anticholinergic drug. The two groups were successfully randomized and there was no statistically significant difference in age (p = 0.375) or ASA physical status classification (p = 0.152) between the two groups, and baseline heart rate was comparable between the groups (p = 0.556). The mean age of the patients in the Atropine + Neostigmine group was 41.27 ± 11.56 years and in Glycopyrrolate + Neostigmine group was

43.22 ± 11.32 years. Baseline heart rates were 78.07 ± 10.36 bpm and 76.92 ± 9.87 bpm, respectively. These similar baseline data allowed to ensure that any differences in outcomes found after the reversal could be confidently attributed to the pharmacological effects of the anticholinergic drugs and not to pre-existing differences between groups, thus enhancing the internal validity of the study.

The most important and clinically relevant result of this study is the high difference in the incidence of tachycardia between the two groups. In the Atropine + Neostigmine group, 40 of 60 patients (66.7%) had tachycardia and none of the 50 patients (0%) in the Glycopyrrolate + Neostigmine group had tachycardia. This difference was highly statistically significant (χ^2 = 52.381, df = 1, p 0.001). This is consistent with known differences in the pharmacology of the two agents. Atropine is a tertiary amine that is

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lipophilic and can enter the blood-brain barrier and has a powerful quick-onset vagolytic activity, often causing a rebound tachycardia especially when coupled with Neostigmine. Given that glycopyrrolate is a quaternary ammonium compound, it is not able to cross the blood brain barrier and has a slower onset of vagolytic action, so avoiding both the bradycardia and excessive tachycardia caused by Neostigmine's rapid effects. This study's findings concur with, and add support to, the findings from a handful of previous clinical studies that have compared the two anticholinergic drugs.

The 1981 study by Mikakur et al. on dose determination of atropine and glycopyrrolate for reversal of neuromuscular blockade was a historic study. They concluded that glycopyrrolate at a dosage of 10 μg/kg with neostigmine resulted in the most stable and consistent heart rate profile without starting with a tachycardia at any tested dosage. On the other hand, atropine with doses of 20 and 30 μg/kg induced significant initial tachycardia with neostigmine. Our findings are similar to the above study which reported a tachycardia rate of 66.7% in the Atropine + Neostigmine group and 0% in the Glycopyrrolate group[11].

In a study of glycopyrrolate versus atropine in the reversal of nondepolarizing neuromuscular block with neostigmine, Ostheimer (1977) reported that glycopyrrolate resulted in a decrease in the incidence of initial tachycardia and arrhythmia. Furthermore, glycopyrrolate was shown to be superior to atropine as an antisialagogue, having more effect on oropharyngeal secretions. These results are consistent with the present study, which also showed good control of secretions in both groups, with a significant cardiovascular benefit observed in the glycopyrrolate group due to the absence of any cases of tachycardia[12].

The current study and literature together clearly show that glycopyrrolate is as effective as neostigmine for the prevention of bradycardia, but is much safer on the cardiovascular system, as it eliminates the risk of tachycardia. Of significance, was the fact that neither Atropine nor Glycopyrrolate had a muscarinic bradycardic effect at all (0% each), confirming that both agents are equally effective at preventing Neostigmine's muscarinic bradycardic effects. The clinical impact of these results is important because tachycardia can lead to a reduction in myocardial oxygen supply, to the onset of myocardial ischemia and to an aggravation of the clinical condition of patients with underlying cardiovascular disease. The present results provide compelling evidence of the advantages of Glycopyrrolate + Neostigmine over Atropine + Neostigmine in anesthetic practice and suggest its use to be preferred for patients with higher cardiovascular risk, including the elderly, the hypertensive and the patient with ischemic heart disease.

This study has some limitations that should be noted when drawing conclusions from the results. The study was conducted at a single institution (PHQ Teaching Hospital, Gilgit) and therefore the findings might not be generalizable to other populations, clinical settings, and geographical areas that could have different patient demographics and anesthetic practices. Secondly, although the sample size of 110 patients is enough to show statistical significance for the primary outcome, it was not large enough to give strong estimates of effect size, and larger multi-centre trials are required to obtain more precise estimates. Third, the number of patients in both groups was not equal: 60 patients in Group A (Atropine + Neostigmine) and 50 patients in Group B (Glycopyrrolate + Neostigmine), which would be better in future studies to reduce any potential bias. Fourth, this study mainly examined cardiovascular outcomes (tachycardia and bradycardia), and other clinically relevant outcomes, including time to extubation, PACU readiness, postoperative nausea and vomiting, oxygen saturation changes, and secretion scoring, were not fully analyzed. Recommendation for further studies the study was performed at one institution on a small sample size of 110 patients and further research should be done at several centres with larger and also equally distributed sample size to enhance the generalizability. The differential group sizes (Group A: 60, Group B: 50) in this study need to be considered in any future studies that might

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replicate this work by employing a formal sample size calculation and an equal size allocation of the groups prior to data collection. This was a study that focused only on the cardiovascular outcomes, and future studies should include more outcome measures, such as time to extubation, PACU readiness, oxygen saturation, secretion scoring, and postoperative nausea and vomiting. In the future, the study should further include patient monitoring for at least 24 hours after surgery as the present study did not monitor the patients after surgery. Patients with cardiovascular disease were not included in this study, and future studies should focus on a separate high-risk group like patients with hypertension or ischemic heart disease to evaluate drug safety in vulnerable patients. This study did not include a subgroup analysis and further research is needed on the effects of these drugs in specific populations like elderly patients, children and obstetric patients.

CONCLUSION

In terms of cardiovascular safety, particularly in terms of preventing tachycardia, this comparison investigation unequivocally shows that glycopyrrolate with neostigmine is substantially better than atropine plus neostigmine. In the Atropine group, the incidence of tachycardia was 66.7%, while in the Glycopyrrolate group, it was 0%. This difference was statistically significant (χ^2 = 52.381, p 0.001). With 0% occurrence in all groups, both medications were equally successful in avoiding bradycardia. The validity of the study was confirmed by the comparability of baseline physiological and demographic data between the groups. In clinical anesthetic practice, glycopyrrolate should be chosen over atropine as the anticholinergic medication of choice for reversing neuromuscular blockade due to its superior hemodynamic stability and total lack of tachycardia, particularly in patients at cardiovascular risk.

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