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ORIGINAL ARTICLE

Comparison between the Effects of Combination of Atropine plus Glycopyrrolate with Atropine alone on Heart Rate for the Reversal of Muscle Relaxant after General Anesthesia

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ABSTRACT

Background: A muscle relaxant is an integral component of general anesthesia. Anticholinesterase drugs employed as their antagonist are associated with certain untoward effects. To counter these undesirable effects, anticholinergic agents, atropine, and glycopyrrolate are often used.

Objectives: To compare and quantify the mean change in heart rate in patients receiving atropine (0.5 mg) alone**,** glycopyrrolate (0.5 mg) alone, and atropine (0.25 mg) plus glycopyrrolate (0.25 mg) after muscle relaxant reversal with neostigmine.

Study Design: Randomized controlled trial

Place and Duration of Study: Department of Anesthesiology and General Surgery Operation Theatre, Nishtar Medical University Multan from 1st January 2021 to 30th June 2021.

Methodology: Ninety patients fulfilling inclusion and exclusion criteria undergoing elective cholecystectomy or ventral hernia repair under general anesthesia were included in this study. Group A (n= 30) received Atropine 0.5mg IV, Group G (n=30) received Glycopyrrolate 0.5mg IV while Group A+G (n=30) received atropine 0.25mg plus glycopyrrolate 0.25mg. Data regarding patients' age, gender, ASA status, type of procedure and operation time, detailed clinical history, and laboratory investigations were taken for all patients. Heart rate of patients before muscle relaxant reversal and after 3 minutes of reversal was noted and heart rate change was calculated.

Results: Mean change in heart rate in group A+G was 9.06±3.55 beats/min, 18.53±9.61 beats/min in group A and 17.26±6.20 beats/min in group G. This difference was statistically significant with a p-value <0.0001.

Conclusion: Atropine and glycopyrrolate combination is more effective than atropine or glycopyrrolate alone in preventing the heart rate variability associated with reversal of neuromuscular blockers using neostigmine.

Keywords: tropine, Glycopyrrolate, Heart rate.

INTRODUCTION

Muscle relaxation is an integral component of general anesthesia as it provides the most favorable condition for securing definitive airway access and ensures optimum surgical conditions.[1] Anticholinesterase drugs such as neostigmine are used as an antagonist to the muscle relaxant. These drugs if used alone are associated with certain untoward effects such as increased secretions and mucus resulting in elevated airway resistance, vomiting, diarrhea, and decreased heart rate.[2-4] To counter these undesirable effects, anticholinergic agents atropine and glycopyrrolate are often used in conjunction with neostigmine.

The published data establishes the fact that the combination of atropine with neostigmine causes a much greater increase in heart rate than the combination of glycopyrrolate with neostigmine.[5,6] It can be especially hazardous in cardiac patients where tachycardia is usually poorly tolerated. Ittichaikulthol et al[7] compared atropine plus glycopyrrolate combination with atropine alone and noted their effects on the heart rate of patients after reversal of muscle relaxants with neostigmine. They found that the mean heart rate increase after 3 minutes of administration of atropine plus glycopyrrolate combination was 22.26±5.5 versus 25.12±7.2 in the atropine group alone. These authors failed to find any statistically significant difference in both groups and concluded that there is no added benefit of giving two anticholinergic drugs, glycopyrrolate and atropine together.[7]

The mechanism of action of glycopyrrolate is quite similar to atropine but it usually causes less tachycardia as compared to atropine.[8] It can thus be hypothesized that a combination of atropine and glycopyrrolate should prevent immediate tachycardia that otherwise would occur and maintaining it for a longer duration.[9] The primary objective of this study is to compare the mean heart rate increase in patients receiving glycopyrrolate plus atropine combination versus using atropine as a sole agent.

The results of this study will help us determine if there is any beneficial effect of giving glycopyrrolate with atropine or giving atropine alone to keep the heart rate in the normal range in preventing neostigmine-induced bradycardia.

MATERIALS AND METHODS

The randomized controlled trial was conducted in the Department of Anesthesiology and General Surgery Operation Theatre was conducted at Nishtar Medical University Multan from January 2021 to June 2021. A total of 90 patients (30 in each group) were selected for this study. Patients aged 20-60 years, both male and female scheduled for elective cholecystectomy or ventral hernia repair under general anesthesia were included in this study. Patients allergic to or have contraindications to any of the study drugs, underlying heart disease, thyrotoxic patients, or patients having tachyarrhythmias were excluded.

Written informed consent was taken from every patient. Patients were divided into three equal groups containing 30 patients in each group. Draw randomization was used for the division of patients. Folded envelopes containing names of the drugs e.g. atropine plus glycopyrrolate, glycopyrrolate alone, and atropine alone were made. Patients were randomly asked to pick one folded paper before surgery. Patients were randomly divided into Group A+G, group G, or group A depending on the folded paper chosen by them. Data regarding patients' age, gender, ASA status, type of procedure, and operation time was calculated. General anesthesia was given by or under the supervision of a consultant Anesthetist.

In Group A+G atropine 0.25 mg plus 0.25 mg glycopyrrolate (half dose of atropine and glycopyrrolate) were given. In Group A 0.5 mg atropine alone was given and in Group G 0.5 mg glycopyrrolate was given. The heart rate of patients before muscle relaxant reversal and after 3 minutes of reversal was calculated.

Data analysis was carried out using SPSS-23. One way-ANOVA was used to compare the stability of mean heart rate between the groups. Tukey HSD was used to see the different groups. Confounder variables such as age, gender, ASA status,

and the duration of surgery were neutralized by stratification. Post-stratification one-way ANOVA test was applied to establish the effect of these confounder variables on the stability of mean heart rate between the groups. P-value <0.05 was taken as statistically significant.

RESULTS

Fifty eight (64.44%) were males and 32 (35.62%) were females with a mean age of 44.6 years. The mean operative time was found to be 49.26min and the mean heart rate at baseline was 77.87/min while the mean change in heart rate was 14.95/min. Out of 90, 68(75.56%) were have ASA I and 22(24.44%) patients were having ASA II and 52 (57.78%) patients underwent cholecystectomy while 38(42.22%) had a ventral hernia repair. One-way ANOVA was applied to determine the difference in mean heart rate between the groups. This difference was found to be statistically significant with a p-value <0.0001 [Table 1].

Tukey HSD test was applied to determine the difference among different groups, there was a significant difference in mean change in heart rate in Group A+G versus group A (P-value <0.0001) and group A+G versus group G (p-value <0.0001). However, there was no significant difference in mean change in heart rate in group A versus group G (P-value 0.75) [Table 2].

Stratification was done based on age, gender, ASA status, duration, and type of surgery, and there was no significant effect of these confounder variables on mean changes in heart rate between the groups. Mean change in heart rate was lower in group A+G as compared to groups A and G [Table 3].

Table 1: Comparison of mean change in heart rate between the groups (One-Way ANOVA)

Heart Rate (Beats/min)	Group A+G	Group A	Group G	F-Ratio	P-value
Mean±SD	9.06±3.55	18.53±9.61	17.26±6.20	16.54	<0.0001

Table 2: Multiple comparison of mean change in heart rate between the different groups (Tukey HSD Test)

(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Group A+G	Group A	-9.4667*	1.786	<0.0001	-13.7266	-5.2067
	Group G	-8.2000*	1.786	<0.0001	-12.4600	-3.9400
Group A	Group A+G	9.4667*	1.786	<0.0001	5.2067	13.7266
	Group G	1.2667	1.786	0.75	-2.9933	5.5266
Group G	Group A+G	8.2000*	1.786	<0.0001	3.9400	12.4600
	Group A	-1.2667	1.786	0.75	-5.5266	2.9933

Table 3: Association of post stratification variables with mean changes in heart rate

Variables		Group A+G	Group A	Group G	F-Ratio	P-value
Age	20-40	8.28	20.11	18.80	10.40	<0.0001
	41-60	9.75	17.85	16.50	6.74	0.002
Gender	Male	15	20.50	18.14	13.29	<0.0001
	Female	8.89	16.28	15.22	4.27	0.024
ASA status	I	9.09	19.20	17.43	11.36	<0.0001
	II	9.0	15.83	16.71	5.99	0.01
Type of surgery	Cholecystectomy	10.11	19.12	17.55	8.7	0.001
	Hernia Repair	7.69	17.76	16.83	7.37	0.002
Duration of surgery	30-50 min	8.68	20.86	17.94	13.42	<0.0001
	>50min	9.5	16.20	16.38	4.54	0.017

DISCUSSION

Neuromuscular blockers cause skeletal muscles paralysis and are an integral component of general anesthesia worldwide in operation theatres and for achieving adequate relaxation in Intensive Care Units.[10, 11] Anesthesiologists and intensivists use them to have favorable conditions for securing definite airway access, providing optimal surgical conditions and facilitating the patients requiring invasive mechanical ventilation.[12]

Neuromuscular blocking agents are reversed by anticholinesterase drugs, the most common being neostigmine and some novel reversal agents, namely sugammadex and calabadion which are gaining popularity. There has been a reported decreased incidence of twenty-four-hour mortality and prolonged coma with acetylcholinesterase inhibitors use.[13] However the use of these drugs comes with several unwanted effects namely decreased heart rate, increased airway resistance, and bowel disturbances. To overcome this phenomenon and to nullify these unpleasant effects, anticholinergic agents (atropine or glycopyrrolate) are usually given in conjunction with neostigmine.[14] Atropine and glycopyrrolate, the two most popular anticholinergic agents of the class, are often administered concurrently to the reversal of nondepolarizing neuromuscular blockers and have antagonistic action mainly on muscarinic 8acetylcholine receptors.[15] Glycopyrrolate, a quaternary ammonium compound has a preferential affinity for the muscarinic M3 receptor, whereas atropine, a tertiary amine, has a lesser affinity for the same.[16]

In the present study, we evaluated the effect of atropine with glycopyrrolate in terms of changes in heart rate variability. We made three groups; in one group we gave 0.5 mg atropine only, in the second group 0.5 mg glycopyrrolate, and in the third group we used a combination of atropine and glycopyrrolate in half doses of 0.25 mg of each drug. We found that a combination of drugs is more effective than individual drugs. Moreover, we did not find any significant difference in the atropine and glycopyrrolate groups. Mean heart rate change was a little less in the glycopyrrolate group as compared to the atropine alone group, although this observed difference among groups was not statistically significant.

Ittichaikulthol et al[7] compared the heart rate variability in patients receiving atropine alone with atropine and glycopyrrolate. The investigators found that the atropine and glycopyrrolate combination is more effective than atropine alone for preventing the mean change in heart rate. In their study mean heart rate after 3 minutes of drug administration was 98.24 beats/min in the atropine alone group and 95.04 beats/min in the atropine plus glycopyrrolate group.

Salem et al. carried out a similar study on 115 patients who received neostigmine with atropine or glycopyrrolate. They figured out that immediately following reversal of muscle relaxant, patients who received 0.9mg glycopyrrolate with neostigmine failed to show any statistically significant heart rate change as compared to patients who received 1.2mg atropine.[5]

Similarly, Tribuddharat et al[17] carried out a double-blinded trial on forty-six patients. To nullify the muscarinic effects of 2.5mg neostigmine, they compared two different doses of atropine, namely 1.2mg with 0.9mg, and concluded that atropine in a dose of 0.9mg could effectively antagonize the parasympathomimetic effects of neostigmine.

Another study by Wetterslev et al[18] compared the heart rate effects of a single dose of 7 micrograms per kilogram of

glycopyrrolate with 2 doses of 8 micrograms per kilogram of atropine at 10 minutes intervals. They figured out that using above mentioned doses caused insignificant heart rate differences and also failed to show any difference in muscarinic effects between these two groups. This trial also favored the idea that a lower atropine dose would cause a lesser increase in heart rate as compared to a higher dose of atropine.[18]

Our study has also some limitations. First, due to the institutional practice and protocols of operation theatre, we failed to blind the anesthesiologist as he must be aware of the identity of the drug to be injected into the patients under anesthesia. Secondly, there were anesthetic factors like the sympathetic response at the culmination of surgery by suctioning, coughing, and bucking on the endotracheal tube and the anesthetic depth before extubation, and other factors that could impact our findings and results. Moreover, in our study, we only included ASA I and II patients and thus we cannot generalize our result findings to other high-risk groups and patients with uncontrolled systemic disease. Therefore additional studies are mandated to effectively establish the atropine and glycopyrrolate combination benefits needed to antagonize the muscarinic effects of neostigmine by appropriate patient selection and dose adjustment.

CONCLUSION

Atropine and glycopyrrolate combination is more effective than atropine or glycopyrrolate alone in preventing the heart rate variability associated with the reversal of neuromuscular blockers using neostigmine.

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