Comparison of Neostigmine-Atropine Administration Methods for Hemodynamic Parameters in Patients Undergoing Elective Surgery: A Randomized Control Trial

Junbei Wu, Huixuan Zhou*

Department of Anesthesiology, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China.

Abstract: **Objective:** The aim of this study is to compare the hemodynamic effects of neostigmine-atropine in the reversal of muscle relaxants when administered either sequentially or simultaneously. **Methods:** Patients undergoing noncardiac surgery were recruited and randomly allocated to either a sequential or a simultaneous administration of neostigmine (0.04 mg kg^{-1}) and atropine (0.02 mg kg−1) at the end of surgery. Sequential group (SEQ group): Neostigmine and 1/3 dose of atropine were administered first minute, followed by another 2/3 dose of atropine 3 minutes later. Simultaneous group (SIM group): Neostigmine and atropine mixture was finished in 4 minutes. The primary outcome was the area under the curve (AUC) of the heart rate difference within 15 minutes of administration. The secondary outcome was the heart rate at each time point and the heart rate difference. **Results:** The AUC of heart rate difference within 15 minutes after administration in the SEQ group was 13.05±9.57 versus 43.56±10.54 in the SIM group (P<0.05). SIM group had a significantly lower heart rate when compared to SEQ group at 9, 10, 11, 12, 13, 14, and 15 minutes after administration (P<0.05). Heart rate difference was significantly smaller at 9, 10, 11, 12, 13, 14, and 15 minutes after administration in the SEQ group (P<0.05). **Conclusion:** Sequential administration, when atropine was administered later, induced smaller heart rate variability. Atropine and neostigmine should be administered in this order: neostigmine combined with small doses of atropine was administered first, followed by the remaining atropine.

Keywords: Neostigmine; Atropine; Heart Rate

Introduction

Postoperative residual curarization is a common problem in post-anaesthesia care units (PACUs) and a risk factor for postoperative complications [1]. Aspiration, airway obstruction, hypoxemia, and postoperative pulmonary complications (PPCs) may be increased by residual curarization..Reversal of neuromuscular blocking agents at the end of surgery is recommended in the guidelines [2]. Neostigmine is commonly administered. Although it is a frequent practice to use the combination of neostigmine and atropine for the reversal of neuromuscular block, heart rate fluctuations are common. Atropine has a more rapid onset than neostigmine, resulting in an initial tachycardia. We performed the present study comparing the hemodynamic effects of two different administration methods for the reversal of residual neuromuscular block in anesthetized patients.

Methods

Study population

Between November 2022 and March 2023, patients having elective non-cardiac surgery at the First Affiliated Hospital of Nanjing Medical University were evaluated for eligibility. Written informed consent was obtained from all patients. All subjects, aged 18 to 75 years, with a BMI in the range of 18.5 to 25.0 kg m^{-2}, who met the criteria for ASA physical status classification I to II, and of expected duration of more than 1 hour under general anesthesia were recruited. We excluded patients with underlying cardiovascular or respiratory diseases, pregnancy, emergent or urgent surgery, contraindication to any study drug or scheduled anesthetic drug.

Randomization and blinding

Based on a computer-generated random distribution sequence (1:1 assignment ratio), participants were randomly assigned to "Sequential group (SEQ group)" or "Simultaneous group (SIM group)". A staff member of the department who was not engaged in the study devised the randomization order prior to the study. Either "SEQ group" or "SIM group" was inscribed on a piece of paper, which was then enclosed in a sealed opaque envelope. The envelopes were then shuffled and labeled.

Study protocol

Standard ASA monitors (electrocardiogram, pulse oximetry, blood pressure, end-tidal CO_2) were applied. Anesthesia was induced with midazolam (0.05 mg kg^{-1}), etomidate (0.3 mg kg^{-1}), sufentanil (0.3 ug kg^{-1}) followed by cis-atracurium (0.2 mg kg^{-1}) intravenously. Anesthesia was maintained with a propofol infusion and/or sevoflurane. Train of four (TOF) was performed for neuromuscular monitoring continuously with the time interval of 30 minutes. During the procedure, a dosage of 0.05-0.07 mg kg-1 of cis-atracurium was administered for intraoperative neuromuscular blockade to keep TOF 0–1.

When the anesthesia team was ready for reversal, they paged the research team to deliver the envelope containing the randomization assignment. The i.v. study drug (neostigmine 0.04 mg kg^{-1} with atropine 0.02 mg kg^{-1}) was administered at the end of surgery once two responses to TOF nerve stimulation were present. SEQ group: Neostigmine and 1/3 dose of atropine were administered first minute, followed by another 2/3 dose of atropine 3 minutes later. SIM group: Neostigmine and atropine mixture is finished in 4 minutes. If the patient's heart rate was below 45 bpm, atropine 0.5mg was administered.

Index

Demographics and clinical characteristics that included age, sex, height, weight, BMI, American Society of Anesthesiologists (ASA) classification were documented before the surgery. Duration of surgery was also recorded. The primary outcome was the area under the curve (AUC) of the heart rate difference (heart rate difference = heart rate - baseline) within 15 minutes of administration. The secondary outcome was the heart rate at each time point within 15 minutes of administration and the heart rate difference.

Statistical analysis

Statistical software SAS was used for data processing. Data were expressed as mean ± standard deviations for continuous variables or n of patients (%) for categorical data. Variance analysis between groups was compared using the two-sample Student’s t-test for continuous variables. The Pearson’s chi-squared or Fisher’s exact test was used to analyze categorical data. The one-way ANCOVA (analysis of covariance) was used to analyze AUC. We used a P value threshold of 0.05 for

statistical significance.

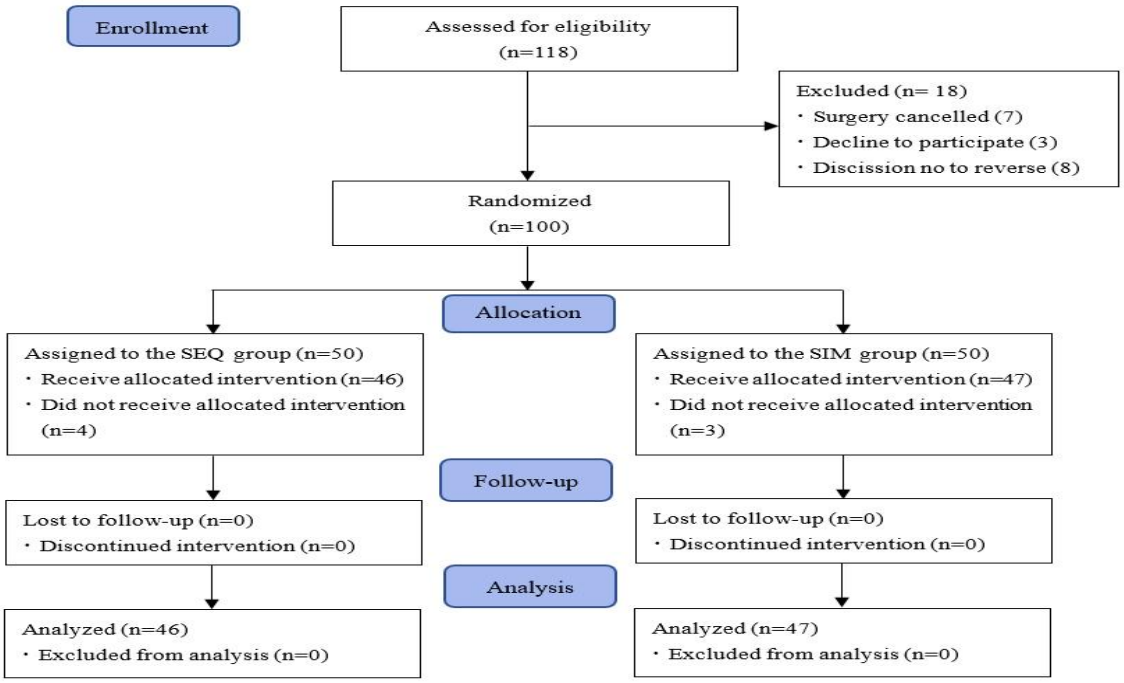

Figure 1. Consort flow diagram of the trial design

Results

(Figure 1) shows the trial design according to Consolidated Standards of Reporting Trials (CONSORT) guidelines. Ninety-three patients (n = 46 SEQ; n = 47 SIM) were finally analyzed. There was not any significant difference between groups in terms of demographic features and duration of surgery (P > 0.05) (Table 1).

Table 1. Demographic and clinical features

	Group	Group	p-value
Age (years)	47.8±11.2	47.0±11.4	0.75
Gender M/F (n)	25/21	20/27	0.26
ASA classification I/II (n)	13/33	18/29	0.31
Height (cm)	165.1±7.3	166.2±8.1	0.48
Weight (kg)	63.8±9.0	65.8±9.2	0.29
BMI (kg/m^2)	23.4±2.7	28.8±2.9	0.47
Duration of Surgery (min)	85.1±18.7	91.2±19.2	0.13

No significant difference was found in baseline heart rate. The AUC of heart rate difference within 15 minutes after administration in the SEQ group was 13.05±8.82 versus 43.56±10.54 in the SIM group (P<0.05). No differences were found in heart rate between the two groups at 1, 2, 3, 4, 5, 6, 7, and 8 minutes after administration (P>0.05). SIM group had a significantly lower heart rate when compared to SEQ group at 9, 10, 11, 12, 13, 14, and 15 minutes after administration (P<0.05) (Figure 2). There was no significant difference in heart rate difference at 1, 2, 3, 4, 5, 6, 7, and 8 minutes after administration (P>0.05). Heart rate difference was significantly smaller at 9, 10, 11, 12, 13, 14, and 15 minutes after administration in the SEQ group (P<0.05) (Figure 3).

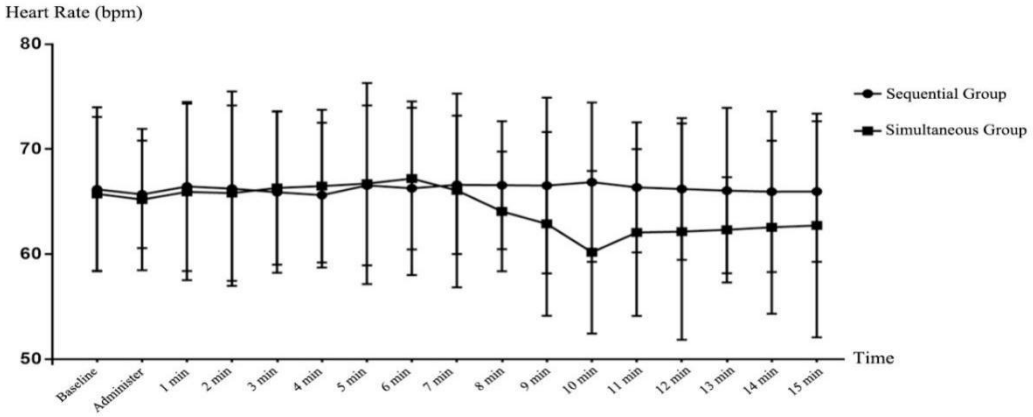

Figure 2. Comparison of heart rate.

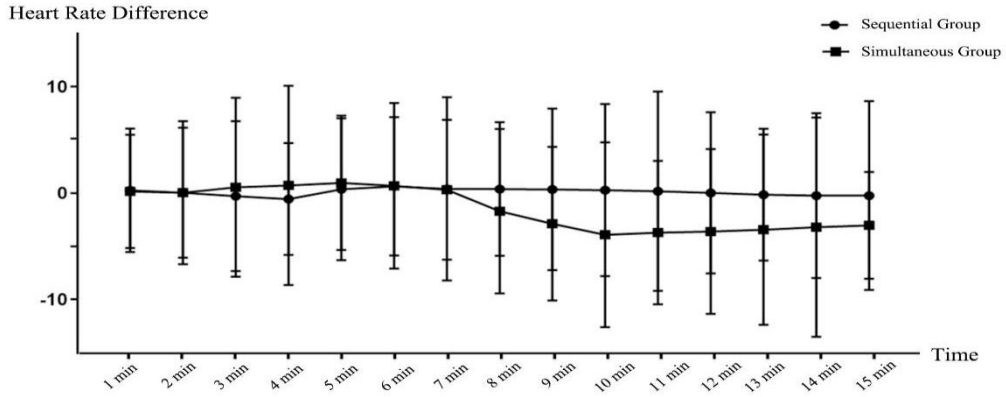

Figure 3. Comparison of heart rate difference

Discussion

By suppressing parasympathetic impacts on the heart, atropine raises the heart rate and improves atrioventricular conduction. The neostigmine-induced bradycardia is correlated with cholinesterase inhibition, or activating cholinergic receptors within the cardiac parasympathetic pathway [3]. the optimal administration mode has not been evaluated.

The effects of atropine develop more quickly than those of neostigmine. The degree and duration of tachycardia were significantly greater when atropine was administered first, followed by neostigmine, than simultaneous administration [4]. When atropine and neostigmine were provided in this order—neostigmine combined with small doses of atropine was administered first, followed by the remaining atropine—no early tachycardia was observed; later bradycardia could be prevented; and no serious arrhythmias had been encountered.

Conclusion

In our study, we observed that there was no significant tachycardia in either group. However, the simultaneous administration of the atropine-neostigmine mixtures subsequently reduced heart rate. Sequential administration, when atropine was administered later, induced smaller heart rate variability. Therefore, we suggest that sequential administration of neostigmine-atropine might be a safe option to reverse neuromuscular blockage. Atropine and neostigmine should be administered in this order: neostigmine combined with small doses of atropine was administered first, followed by the remaining atropine.

References

[1] Naguib M, Kopman AF, Ensor JE. Neuromuscular monitoring and postoperative residual curarisation: A meta-analysis. BJA. [J] British Journal of Anaesthesia. 2007;98:302-316.

[2] Thilen SR, Weigel WA, Todd MM, et al. 2023 american society of anesthesiologists practice guidelines for monitoring and antagonism of neuromuscular blockade: A report by the american society of anesthesiologists task force on neuromuscular blockade. [J] Anesthesiology. 2023;138:13-41.

[3] Backman SB, Stein RD, Blank DW, et al. Different properties of the bradycardia produced by neostigmine and edrophonium in the cat. [J] Canadian Journal of Anaesthesia. 1996;43:731-740.

[4] Ovassapian A. Effects of administration of atropine and neostigmine in man [J], Anesthesia & Analgesia. 1969;48:219-223.