Recovery of diaphragm function after neuromuscular block by means of diaphragm ultrasonography with comparison of neostigmine vs normal saline as reversal drugs

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Abstract

Background

Residual neuromuscular blockade (RNMB) is a well-known risk factor after general anesthesia for critical respiratory events and higher postoperative morbidity. Acetylcholinesterase inhibitors cannot completely avoid RNMB. Neuromuscular monitoring of the adductor pollicis is the gold standard for detecting RNMB, but it cannot be carried out on conscious patients. Ultrasonography of diaphragm excursion may reveal residual effects of neuromuscular blocking agents in conscious patients.

Methods

This prospective, double-blind, single-center randomized controlled study enrolled 150 patients, who belong to ASA physical status I and II, aged 18–65 years, and be scheduled to undergo neuromuscular block with cis-atracurium for neurosurgery. The primary objective will be to compare the difference in DE between groups. Patients will be extubated when the train-of-four ratio is ≥ 0.9. Diaphragm ultrasonography will be used to evaluate the diaphragm excursion. The Diaphragm ultrasonography will be performed before anesthesia induction, at one minute after extubation, and before being discharged from the PACU. The secondary objective was to compare the incidence of postoperative pulmonary complications after operation.

Results

After extubation, the DE of patients was significantly larger in the NEO group than in the NS group (14.14 ± 1.93 vs. 12.96 ± 1.62 mm, $P < 0.05$). The incidence of RNMB was higher in the NS group, when compared to the NEO group, after extubation (73.33% vs. 53.33%, $P = 0.011$) and when leaving the PACU (33.33% vs. 20%, $P = 0.044$). The incidence of respiratory insufficiency after extubation was higher in the NEO group (14.67%), when compared to the NS group (4%) ($P = 0.046$).

Conclusion

Residual neuromuscular blockade is still a problem to be solved. Diaphragm ultrasound may become a bedside tool in the neuromuscular monitoring field to detect underestimated residual neuromuscular blockade after neuromuscular block.

Trial registration:

The trial was registered prior to patient enrollment at ClinicalTrials.gov (ChiCTR1900021095, Date of registration: January 28, 2019).

Introduction

It has been widely recognized that the use of neuromuscular blocking agents in clinical care facilitates intubation and revolutionized surgery [1]. However, incomplete recovery from neuromuscular blockade after anesthesia and surgery continues to be a common problem worldwide. Furthermore, the use of neuromuscular blocking agents (NMBAs), the reversal agents, and respiratory outcome after surgery remains as a subject of research and debate [2, 3]. It has been suggested that RNMB is associated with postoperative pulmonary complications (PPCs), which are the main cause of death, and increase the hospital care expenditures in various operations [4]and higher postoperative morbidity after general anesthesia [5, 6]. The study conducted by Bulka et al [7] revealed that the intraoperative use of intermediate nondepolarizing NMBAs is associated with the development of pneumonia after surgery. Among patients who received these agents, non-reversal was associated with increased risk of postoperative pneumonia.

Diaphragm dysfunction leads to respiratory complications, and can prolong the duration of mechanical ventilation. The ultrasound of the diaphragm allows for the direct visualization of the diaphragm muscle, and assessment of its activity [8]. Sonographic evaluation of the diaphragm has been used to predict the outcome after extubation in the ICU. The role of ultrasound in the assessment of diaphragm function has been investigated [9] with the rationale that the diaphragm plays a crucial role in respiratory muscle endurance. Diaphragmatic ultrasound is non-invasive, can easily performed, and is a reliable tool for assessing diaphragm excursion. The present study aimed to compare diaphragmatic excursion (DE) after administration of neuromuscular blocking agents and its reversal drugs. And we observe the incidence of postoperative pulmonary complications after operation.

Methods

Study design and eligibility

This study is a prospective, double-blind, randomized controlled trial involving 150 patients aged 18-65years, with American Society of Anesthesiologists (ASA) physical status I-II, with a body mass index (BMI) of < 28kg/m^2, who will receive cis-atracurium for elective neurosurgery under general anesthesia. Exclusion criteria: patients with pulmonary dysfunction (e.g. bronchial asthma, pneumothorax, chronic obstructive pulmonary disease, restrictive pulmonary disease, and other pleural disease), patients with liver or kidney insufficiency, and patients with neuromuscular diseases. Patients with diaphragm dysfunction, and those who were under an unstable internal environment were excluded during the study period. Considering the accuracy of the measurement, patients with cervical spine injury, and those with a surgical history of hand or forearm trauma were also excluded.

Randomization

Written informed consent was obtained during the preoperative evaluation. All patients know the treatment plan and adverse reactions. Afterwards, each patient was randomly allocated to either the

neostigmine (NEO) group or normal saline (NS) group. Randomization were performed using a table created on www.randomization.com. The allocation plan was carried out using a variable block randomization method 1:1 to distribute the patients equally to each group.

Intervention plan

The anesthetic technique will be standardized for all patients. The induction will be achieved with fentanyl of 2-4ug/kg, propofol of 2-2.5mg/kg, and cis-atracurium of 0.2mg/kg. Orotracheal intubation will be performed after the patient fails to register signals using TOF. Anesthesia was maintained with sevoflurane, remifentanil and propofol. The patient was monitored with non-invasive blood pressure, electrocardiography, pulse oximetry, capnography, and bispectral index (BIS) during surgery. The BIS values were maintained within 40-60 throughout the anesthesia. All patients undergone neuromuscular monitoring with ulnar nerve stimulation using the TOF-Watch preoperatively.

Prior to induction of anesthesia, the baseline DE will be evaluated by one operator skilled in ultrasonography. The operator will use a 3.5-5.0 MHz US convex array probe in the supine position during quiet breathing. With the liver serving as an acoustic window, the probe will be placed below the right costal margin in the mid-clavicular line. The two-dimensional model will be initially used to obtain the best approach, and select the exploration line. Then, the M-mode will be used to display the motion of the anatomical structures along the selected line [10,11]. A complete breathing cycle should be included in one image. In the M-mode, the lowest point is the depth of the diaphragm movement at the end of inspiration. The highest point is the depth of diaphragm movement at the end of expiratory. The distance between the highest and lowest point of diaphragm movement is the DE. All parameters were measured for three times, and the average values were used for the final data analysis. Ultrasonic observation of the left diaphragm remains difficult, and has a low success rate. This is mainly due to the hollow organs, such as the stomach below the left diaphragm, which are often interfered by containing a large amount of gas. At the same time, the spleen, as a reference sound window, is significantly smaller than the liver, which affects the examination [12]. Therefore, we chose the right diaphragm for the measurement.

At the end of operation and when TOF shows a minimum of two twitches, patients will receive the reversal drug according to the allocation. Patients in the NEO group will receive 50 μg/kg neostigmine and 15 μg/kg atropine, while those in the NS group will receive 10 ml normal saline. Extubation will be performed when the following criteria are met: (1) the patient is awake, and can execute simple commands; (2) the patient's respiratory pattern is regular, with a tidal volume of 6-7 mL/kg referred to the ideal body weight; (3) the TOF ratio is≥0.9. The diaphragm excursion (DE) will be measured at one minute after extubation and before discharge from the PACU. Arterial blood gas will be collected after extubation within one minute, and upon discharge from the PACU in both groups. The DE of patients in the two groups will be measured by a doctor who is blinded to the assignment, and specifically trained to carry out the diaphragm ultrasound according to Vivier's technique [13].

Follow-up will be performed to document adverse events and complications after 7 and 30 days postoperation. According to literature, the definition of postoperative pulmonary complication is as following. Suspected pneumonia [14,15]: when patient was treated with antibiotics for respiratory infection, plus at least one of the following criteria: new or change in sputum; new or change in lung opacities on a clinically-indicated chest radiograph; temperature >38.3°C; leukocyte count >12 × 10^9/L. Hypoxia [6]: $SpO_2 \leq 93\%$ with or without supplemental oxygen administration in the PACU. Hypercapnia [16]: $PaCO_2 \geq 46$ mmHg upon extubation and discharge from the PACU. Respiratory insufficiency: Hypercapnia and PaO2/FiO2≦300 after extubation. Patient was defined as having postoperative pulmonary complication, if they met at least one of these criteria after surgery.

The primary objective will be to compare the difference in DE between NEO and NS group. The secondary outcome will be to compare the incidence of postoperative pulmonary complications, including hypoxemia, hypercapnia, postoperative pneumonia, and respiratory insufficiency.

Statistical analysis

The sample size was estimated based on the results of the preliminary experiments. Based on a 5% level of statistical significance and a power of 85%, the minimum sample size required was 75 patients per group (a total of 150 patients). Data analysis was performed using SPSS version 22. Frequency and percentage were used to describe the counting data, and these were compared between groups using Chi-square test or Fisher's exact test. Measurement data were presented as mean ± standard deviation, and t-test was used to compare the values between groups. Repeated-measures analysis of variance (ANOVA) was performed to analyze the time-dependent data. A *P*-value of less than 0.05 was considered statistically significant.

Results

A total of 186 cases met the inclusion criteria in the China-Japan Friendship Hospital from September 2018 to April 2019. The types of operations included microvascular decompression of the facial nerve, trigeminal nerve and glossopharyngeal nerve through the posterior cranial fossa. Finally, 150 cases were enrolled for the present study. Figure 1 presents the reasons for exclusion for the present study.

The patient demographics and clinical characteristics are presented in Table 1. The patient's gender, age, BMI, American Society of Anesthesiologists physical status, smoker was not significantly different between groups ($P > 0.05$). There were not different in NMBAs dosage and anesthetic time between groups. When patients received different reversal methods, their PACU time, hospital length of stay were not significantly different between groups ($P > 0.05$).

Table 1
Patient demographics and clinical characteristics

Characteristic NEO		**NS Total**		***P*-value***
(N = 75)		**(N = 75)**	**(N = 150)**	
Male sex-no.(%)	26(34.67)	21(28.0)	47(31.33)	0.379
Age, median ± sd-yr	51.93 ± 10.59	51.15 ± 9.30	51.54 ± 9.94	0.630
BMI, median ± sd-kg/m^2	24.22 ± 2.88	24.36 ± 2.90	24.29 ± 2.88	0.761
ASA, I/II-no.	34/42	37/38	71/79	0.572
Comorbidities-no. (%)				
Hypertension	15(2.0)	15(2.0)	30(2.0)	1.000
Diabetes	1(1.33)	5(6.67)	6(4.0)	0.000
Arrhythmia	1(1.33)	1(1.33)	2(1.33)	1.000
Cerebral infarction	0	2(2.67)	2(1.33)	0.497
Smoker-no.(%)	2(2.67)	5(6.67)	7(4.67)	0.442

*Independent Student's *t*-test was used to compare the means, and Chi-square test or Fisher's exact test was used to compare the proportions.

Table 2
Outcomes after treatments receive according enrollment

Characteristic	NEO	NS	Total	*P*
NMBAs dosage, mg	15.88 ± 3.11	15.50 ± 2.99	15.69 ± 3.05	0.448
Anesthetic time, minutes	88.63 ± 15.98	88.40 ± 15.00	88.51 ± 15.45	0.929
PACU time, minutes	48.33 ± 13.59	47.20 ± 11.98	47.77 ± 12.78	0.589
Hospital length of stay, days	6.79 ± 2.21	6.05 ± 1.79	6.42 ± 2.04	0.027
Diaphragm excursion, mm				
Baseline	12.86 ± 1.43	13.14 ± 1.87	13.00 ± 1.65	0.314
After extubation	14.14 ± 1.93	12.96 ± 1.62	13.55 ± 1.78	0.000
Discharged from PACU	13.00 ± 1.68	12.93 ± 2.40	12.97 ± 2.04	0.831
RNMB, no. (%)				
After extubation	40(53.33)	55(73.33)	95(63.33)	0.011
Discharged from PACU	15(20.0)	25(33.33)	40(53.33)	0.044
Blood Gas				
$PaCO_2$, mmHg	46.03 ± 7.02	44.39 ± 6.23	45.21 ± 6.67	0.134
After extubation	38.69 ± 4.76	38.42 ± 4.76	38.55 ± 4.52	0.714
Discharged from ACU	< 0.001[a]	< 0.001[a]		
P values				
PaO_2, mmHg	184.25 ± 80.05	202.85 ± 72.20	193.55 ± 76.54	0.137
After extubation	187.53 ± 69.60	189.09 ± 60.46	188.31 ± 64.98	0.884
Discharged from PACU				
Lac, mmol/L	0.95 ± 0.41	0.98 ± 0.68	0.96 ± 0.56	0.784
After extubation	0.99 ± 0.45	0.95 ± 0.34	0.97 ± 0.40	0.543
Discharged from PACU				

The DE of patients was significantly larger at one minute after extubation in the NEO group, when compared to the NS group ($P < 0.05$). Furthermore, the incidence of RNMB was higher in the NS group, when compared to the NEO group, after extubation (73.33% vs. 53.33%, $P = 0.011$) and when leaving the PACU (33.33% vs. 20%, $P = 0.044$).

There was no difference in $PaCO_2$ between the groups after extubation and upon leaving the PACU. For the NEO group, the $PaCO_2$ was significantly higher after extubation, when compared to that upon leaving the PACU ($P < 0.001$). The same trend was also found in the NS group.

The data of postoperative pulmonary complications was presented in Table 3. Pneumonia occurred in 1.55% of patients at seven days after the operation, and in 6.2% of patients at 30 days after the operation. The results exhibited a sharp downward trend in terms of the incidence of hypercapnia after a period of postoperative time. A total of 13 patients (8.67%) developed hypoxemia in the PACU, and 9.33% of patients had respiratory insufficiency after extubation. However, there was no significant difference in the incidence of pneumonia, hypoxemia and hypercapnia ($P > 0.05$). The incidence of respiratory insufficiency after extubation was higher in the NEO group (14.67%), when compared to the NS group (4%) ($P = 0.046$)

Table 3
Postoperative pulmonary complications

Characters	NEO	NS	Total	*P*-values
Postoperative pneumonia, no. (%)				
7 days	1(1.49)	1(1.61)	2(1.55)	1.000
30 days	5(7.46)	3(4.84)	8(6.20)	0.719
Hypoxemia, no. (%)	6(8.0)	7(9.33)	13(8.67)	0.772
Hypercapnia, no. (%)				
After extubation	36(48.0)	33(44.0)	69(46.0)	0.623
Discharged from PACU	2(2.67)	3(4.0)	5(3.33)	1.000
Respiratory insufficiency, no. (%)	11(14.67)	3(4.0)	14(9.33)	0.046

Discussion

RNMB remains as a significant factor in the causation of postoperative pulmonary complications, and is often underestimated by anesthesiologists. Acceleromyography is the recommended clinical tool to monitor a muscular blockade. Although this has been strongly advocated, this approach remains uncomfortable for conscious patients when assessing the RNMB. Quantitative monitoring is not routinely and intraoperatively used, and in any case, it does not rule out the possibility of muscle weakness in the postoperative period [17, 18]. Despite the use of neostigmine reversal, RNMB may still occur. Quantitative monitoring suggests that after intermediate-acting nondepolarizing NMBA use, up to 60% of patients may have a clinically meaningful RNMB [19, 20]. However, the determination of whether the technique is a valid method for neuromuscular evaluation has become a major subject for debate.

Diaphragm ultrasound can be an effective alternative. The introduction of ultrasound makes the assessment of the function of the main respiratory muscle (the diaphragm) possible using a noninvasive, bedside, repeated, safe and radiation-free tool [21]. After the use of NMBAs, the diaphragm lastly relaxes, and initially recovers [22]. Diaphragm dysfunction is associated with respiratory insufficiency, hypoxia, atelectasis, and prolonged mechanical ventilation, ICU and prolonged hospital stay [23, 24]. Therefore, the evaluation of diaphragm function is helpful to reduce the occurrence of postoperative pulmonary complications.

In the present study, the investigators attempted to assess diaphragm function in conscious patients using ultrasound. The data revealed that the DE was significantly higher in the NEO group than in the NS group after extubation. Furthermore, upon leaving the PACU, in the NEO group, this tended to the complete recovery of where the baseline diaphragm excursion occurred. And Cappellini et al. performed a study in patients who, after rocuronium administration, received neostigmine or sugammadex: the authors found an early (0 min) but not long-lasting (30 min) association between diaphragm failure and recovery drug treatment [25]. Those outcomes may be suggested the reversal drugs can be helpful to the recovery of muscle function after use of neuromuscular blocking agents during early period of postoperation.

Postoperative pneumonia is a dominating hospital-acquired infection worldwide [26, 27]. Pneumonia has been associated with related mortality, longer hospital stay, more postoperative hospital readmissions, and increased health costs [28, 29]. In the present study, the investigators chose postoperative pneumonia as one of the follow-up outcomes. Among the 150 patients, 21 patients were lost follow up, in which 8 patients were from the antagonized group and 13 patients were from the unantagonized group, with a loss rate of 14%. The reasons were, as follows: (1) the patients could not be contacted; (2) the information of postoperative nursing records was incomplete; (3) there were defects in the laboratory results. In the data analysis, the available data, including hypoxemia, hypercapnia and respiratory insufficiency, were included in the statistical analysis, except for missing postoperative pneumonia information. There was no statistical difference in demographic characteristics between the patients who were lost follow-up and those who were included in the present study. The incidence of PPCs was similar for the two groups. Furthermore, 13 patients had hypoxemia in the PACU (8.67%). After extubation, the incidence of hypercapnia was 46%, and the incidence decreased to 3.33% when they left the PACU. Moreover, 9.33% of patients had respiratory insufficiency after extubation. However, the incidence of respiratory insufficiency after extubation was higher in the NEO group, when compared to the NS group during postoperative follow-up. With neostigmine, RNMB cannot always be excluded, especially when an intermediate or long-lasting muscle relaxant is administered. Reversal of NMBAs with neostigmine leads to neostigmine-induced RNMB [30, 31]. Neostigmine does not improve the oxygenation of patients in PACU and was associated with an increased incidence of postoperative atelectasis [32]. Neostigmine administered in the rats after recovery of TOF impairs upper airway integrity and genioglossus and diaphragm muscle function [33]. High dose of neostigmine (over 60ug/kg) increases the risk of respiratory complications unrelated to the effects of NMBAs [34]. Maybe it’s more important that the timing and

reasonable dosage of neostigmine. In recent years, conflicting data have indicated that the use of reversal agents or Acceleromyography monitoring could not decrease the risk of PPCs.

Due to anatomical reasons, diaphragm movement is often interfered during thoracic and abdominal surgery. Therefore, the reasons for postoperative diaphragm dysfunction remain complex and uncertain. As far as this kind of surgery is concerned, part of the reasons of PPCs come from the influence of the operation itself. In ruling out this kind of operation, focus should be given in analyzing the relationship among neuromuscular blocking agents, diaphragm function, and postoperative pulmonary complications. The present study had some limitations. Primarily, the investigators only enrolled patients who had ASA physical status I or II, were within 18–65 years old, and had no lung disease. The other conditions of these patients could not be determined, such as advanced age, obesity, or the presence of chronic obstructive pulmonary disease. Furthermore, neurosurgery had a lower incidence of PPCs, when compared to thoracoabdominal surgery. The next step is to expand the research population and types of operation, in order to further research the relationship of DE and postoperative pulmonary complications.

In conclusion, RNMB is still a frequent and risky postoperative adverse reaction after the administration of NMBAs. The reversal drugs may be helpful to the recovery of diaphragm function, however it cannot reduce the incidence of PPCs. Diaphragm ultrasound could be an attractive, non-invasive, promising tool to evaluate diaphragm function after neuromuscular blockade. More research will be needed to optimize the peri-operation management.

Abbreviations

RNMB: residual neuromuscular blockade; DE: diaphragm excursion

ASA: American Society of Anesthesiologists; PACU: post-anesthesia care unit

NEO: neostigmine; NS: normal saline; PPCs: postoperative pulmonary complications

NMBAs: neuromuscular blocking agents; ICU: intensive care unit;

BMI: body mass index; TOF: Train of four; BIS: body mass index

Declarations

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Authors’ contributions

Yiqing Yin, Xuejiao Chen and Quanyong Yang designed and conceived of the study, performed the statistical analysis and drafted the manuscript. Qian Pan and Zhenzhen participated in collecting data. Xuejiao Chen and Quanyong Yang were same for the contribution to this article. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Written informed consent will be obtained from all participants. The China-Japan Friendship Hospital Research Ethics Committee approved the present protocol of study with registration number 2018-96-K70.

Consent for publication

Written informed consent was obtained from all participants including consent for publication.

Competing interests

The authors declare that they have no competing interests.

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Figures

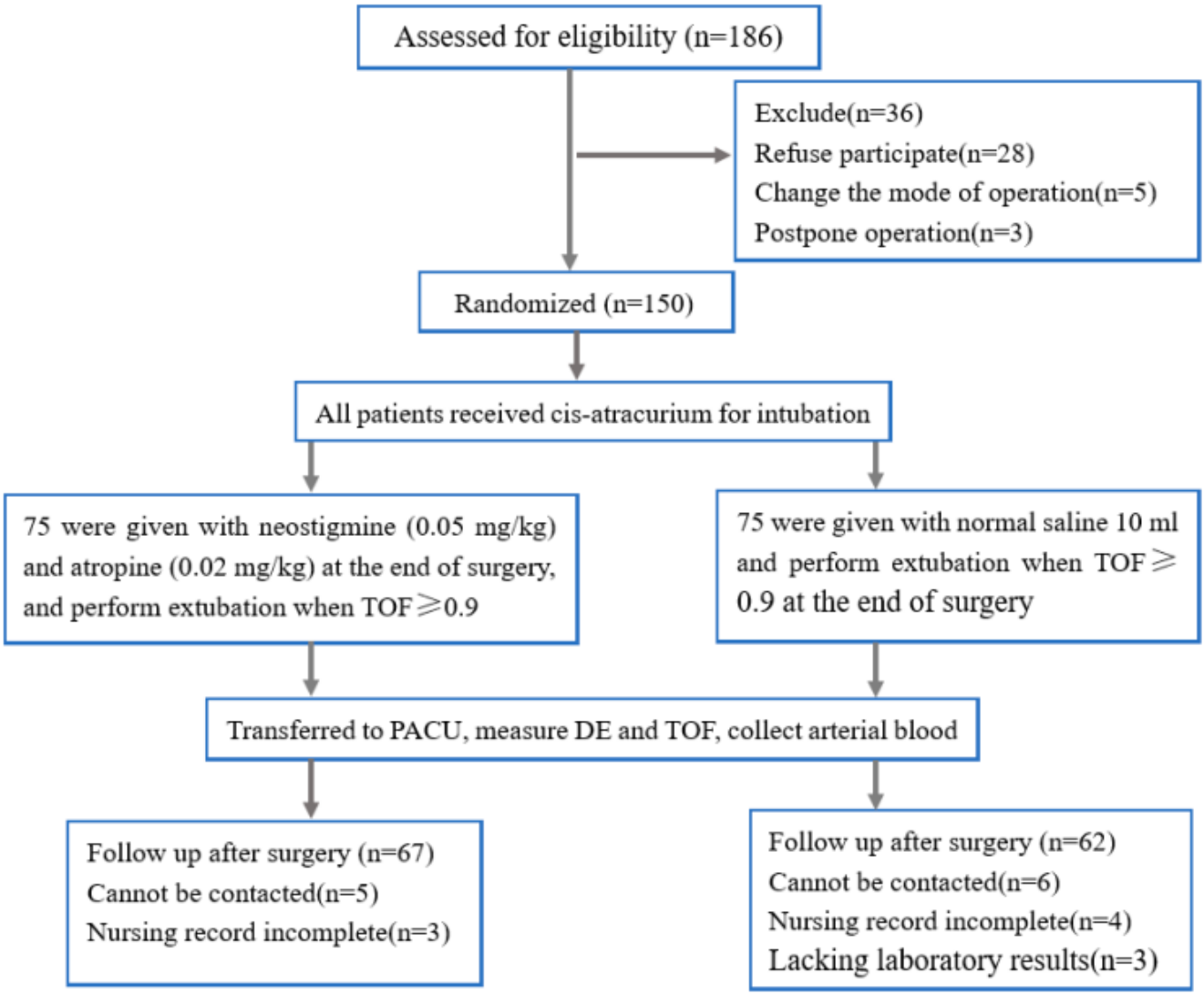

Figure 1: A flow chart in the study

Figure 1

See image above for figure legend