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ORIGINAL ARTICLE

Optimizing Neostigmine Dosing for Neuromuscular Blockade Reversal: A Randomized Controlled Trial Assessing Diaphragmatic Recovery After Laparoscopic Cholecystectomy

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Background

Residual neuromuscular blockade (RNMB)can impair diaphragmatic function and increase the risk of postoperative respiratory complications, especially after laparoscopic procedures where ventilatory mechanics are already compromised. Neostigmine is still the most frequently employed reversal agent, but its optimal dosing balancing efficacy and side effects has not been clearly established. This study aims to assess whether a lower neostigmine dose (0.04mg/kg) restores diaphragmatic function as effectively as the standard dose (0.08mg/kg), while minimizing cholinergic side effects, in patients undergoing elective laparoscopic cholecystectomy.

Methods

In a double-blind, randomized controlled trial, 50 ASA I–II adult patients were assigned to receive either full-dose or half-dose neostigmine, each with atropine (0.02mg/kg), at a train-of-four (TOF) count ≥2. Diaphragmatic function was assessed using bedside ultrasonography measuring diaphragmatic excursion (DE) and diaphragmatic thickening fraction (DTF) at baseline, and at 0, 10 and 30 minutes after reversal. Secondary outcomes included arterial blood gases (ABGs), hemodynamic and respiratory variables, cholinergic side effects, and post-anesthesia care unit (PACU) stay.

Results

Both groups showed a significant postoperative reduction in DE and DTF ($p<0.001$), with no statistically significant differences between groups. The full-dose group exhibited significantly higher rates of vomiting (48% vs. 16%), bradycardia (40% vs. 12%), and salivation (48% vs. 20%) ($p<0.05$). ABG values, hemodynamics, and PACU duration were similar between groups.

Conclusion

A reduced neostigmine dose (0.04mg/kg) provides equivalent diaphragmatic recovery compared to the standard dose, with fewer cholinergic side effects. These findings support a monitoring-guided, individualized approach to neuromuscular block reversal in low-risk patients.

Keywords

Diaphragm, Laparoscopic cholecystectomy, Neostigmine, Neuromuscular blockade, Postoperative recovery, Reversal agents, Ultrasonography.

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INTRODUCTION

Laparoscopic cholecystectomy is the treatment of choice for gallbladder disease because its minimally invasive approach results in less postoperative pain, shorter hospital stays, and quicker recovery compared to open surgery[1,2]. Despite these advantages, transient postoperative diaphragmatic dysfunction remains a concern. Factors such as CO_2 pneumoperitoneum, patient positioning, anesthetic agents, and residual neuromuscular blockade (rNMB) can impair respiratory mechanics and increase the risk of postoperative pulmonary complications (PPCs)[3–5].

Neuromuscular blocking agents (NMBAs) are routinely used to assist with endotracheal intubation and maintain optimal conditions during surgery[6]. However, residual effects of NMBAs particularly involving the diaphragm can persist postoperatively, even after apparent peripheral recovery. This may lead to hypoventilation, atelectasis, or delayed emergence from anesthesia[7,8].

By inhibiting acetylcholinesterase and raising acetylcholine concentrations at the neuromuscular junction, neostigmine is commonly utilized to reverse non-depolarizing neuromuscular blockade. It is often co-administered with antimuscarinic agents such as atropine to offset cholinergic side effects including bradycardia, excessive salivation, and gastrointestinal disturbances[9]. Traditional neostigmine doses range between 0.04 and 0.08mg/kg; however, recent literature suggests that lower doses may be sufficient when administered after partial spontaneous neuromuscular recovery, potentially reducing side effects without compromising efficacy[10,11].

Importantly, traditional TOF monitoring at peripheral muscles like the adductor pollicis does not necessarily reflect diaphragmatic recovery, as the diaphragm often exhibits distinct pharmacodynamic and recovery characteristics[12]. Therefore, targeted assessment of diaphragmatic function is necessary for a more accurate evaluation of postoperative respiratory performance.

Ultrasonography has emerged as a non-invasive, reliable bedside tool to assess diaphragmatic motion and contractility, using parameters such as diaphragmatic excursion (DE) and diaphragmatic thickening fraction (DTF)[13–15]. These ultrasound-derived metrics correlate with respiratory performance and have been validated as predictors of extubation readiness and respiratory adequacy in both critical care and perioperative settings[16,17].

Transient diaphragmatic dysfunction after anesthesia and surgery is not only a physiologic observation but may contribute to clinically relevant events including hypoventilation, atelectasis, and other postoperative pulmonary complications (PPCs); in at-risk patients this can lead to prolonged oxygen therapy or re-intubation. These clinical sequelae motivate the need to assess diaphragmatic recovery specifically rather than relying solely on peripheral TOF indices[12].

Despite the widespread use of neostigmine, few studies have compared different dosing strategies using diaphragm-specific functional endpoints. Therefore, this study aimed to evaluate the effects of two neostigmine doses 0.08mg/kg and 0.04mg/kg on diaphragmatic recovery after laparoscopic cholecystectomy, using ultrasound as an objective assessment method. We hypothesized that a reduced dose would provide equivalent recovery with fewer cholinergic side effects.

METHODOLOGY

Study Design and Ethical Considerations:

This prospective, randomized, double-blind, parallel-group controlled trial was carried out at Aswan University Hospital between October 2022 and April 2023. The study protocol received approval from the Institutional Review Board (Approval No. 944/7/24) and was registered on ClinicalTrials.gov (NCT06787638). All procedures adhered to the ethical standards of the Declaration of Helsinki, and written informed consent was obtained from each participant before enrollment.

Participants:

A total of 50 adult patients (aged 18–60 years) with American Society of Anesthesiologists (ASA) physical status I or II were enrolled in the study. All participants were scheduled to undergo elective laparoscopic cholecystectomy under general anesthesia.

Exclusion Criteria:

- Body mass index (BMI) >35kg/m².
- Known neuromuscular or diaphragmatic disorders.
- Significant pulmonary disease (e.g., COPD, restrictive lung disease).
- Pregnancy or breastfeeding.
- Known hypersensitivity to neostigmine or atropine.
- History of bradyarrhythmia or conductionabnormalities.
- Renal or hepatic insufficiency.

Randomization and Blinding:

Patients were randomly allocated into two equal groups (n= 25 per group) using a computer-generated randomization sequence. Allocation concealment was ensured using sealed, opaque, sequentially numbered envelopes prepared by a third party.

• *Group F (Full-dose group):* Received neostigmine 0.08mg/kg with atropine 0.04mg/kg.

• *Group H (Half-dose group):* Received neostigmine 0.04mg/kg with atropine 0.02mg/kg.

Both the patients and the investigator performing diaphragmatic ultrasound assessments were blinded to group allocation. Drug preparation and administration were carried out by an anesthesiologist not involved in outcome evaluation.

Anesthetic Technique:

All patients received standard premedication and were preoxygenated for 3 minutes. ASA monitoring, including ECG, non-invasive blood pressure, SpO_2, and capnography, was applied. General anesthesia was induced with propofol (2.5mg/kg), fentanyl (2μg/kg), and rocuronium (0.6mg/kg) to achieve neuromuscular blockade.

Tracheal intubation was performed after confirmation of adequate neuromuscular relaxation. Anesthesia was maintained with sevoflurane in a 50% oxygen-air mixture. Added 1gram paracetamol plus ondansetron 8mg and 8mg dexamethasone as antiemetic, additional rocuronium boluses were administered intraoperatively as needed.

Intraoperative neuromuscular monitoring was conducted using train-of-four (TOF) stimulation at the adductor pollicis muscle via a peripheral nerve stimulator (Fisher and Paykel Healthcare Innervator NS252). Neuromuscular reversal was administered once the TOF count reached ≥2. Extubation occurred only after achieving a TOF ratio ≥0.9 and confirming adequate spontaneous ventilation and patient responsiveness.

Intervention:

Each group received the allocated neostigmine-atropine combination intravenously over 60 seconds, immediately after TOF count reached ≥2. At the end of surgery, neuromuscular blockade was reversed using intravenous neostigmine at either 0.04mg/kg or 0.08mg/kg according to group allocation. Atropine sulfate was co-administered in a dose of 0.02mg/kg for the 0.04mg/kg neostigmine group and 0.04mg/kg for the 0.08mg/kg neostigmine group, maintaining a 1:2 ratio between atropine and neostigmine, as per standard recommendations to mitigate muscarinic side effects. All drugs were prepared by an anesthesiologist not involved in outcome assessments.

Ultrasound Assessment of Diaphragmatic Function:

Diaphragmatic function was assessed using point-of-care ultrasound (POCUS) by single an experienced anesthesiologist blinded to group allocation. Two key parameters were evaluated:

1. Diaphragmatic Excursion (DE):

• Measured with a 3.5–5MHz curvilinear probe (ACUSON NX3, Siemens, Germany) in the right subcostal region in M-mode during quiet breathing.

• Values recorded in centimeters (cm).

2. Diaphragmatic Thickening Fraction (DTF):

• Measured using a 7–12MHz linear probe (ACUSON NX3, Siemens, Germany) at the zone of apposition.

• DTF was calculated using the formula: DTF (%)= [(Thickness at end-inspiration−Thickness at end-expiration) / Thickness at end-expiration]×100.

Ultrasound measurements were performed at the following time points:

• T0: Pre-induction baseline.

• T1: Immediately post-reversal (0 minutes).

• T2: 10 minutes after reversal.

• T3: 30 minutes after reversal.

Each measurement was performed in triplicate, and the average value was used for analysis to improve precision.

Secondary Outcomes:

• *Hemodynamic variables*: Heart rate and mean arterial pressure (MAP) Immediately post-reversal (0 minutes),10 minutes after reversal and 30 minutes after reversal.

• *Respiratory variables:* Peripheral oxygen saturation (SpO_2) Immediately post-reversal (0 minutes),10 minutes after reversal and 30 minutes after reversal.

• *Arterial blood gases (ABGs)*: pH, PaO_2, $PaCO_2$ (drawn at 30 minutes post-reversal).

• *Cholinergic side effects:* Nausea (a central, subjective feeling of the urge to vomit), vomiting (Reflexive expulsion of stomach contents via the mouth), salivation (Reflex secretion of saliva, often parasympathetically mediated), bradycardia (HR <50bpm).

• *Post-anesthesia care unit (PACU) stay* (modified Aldrete score was >9).

All complications and side effects were recorded and managed according to standard protocols.

Sample Size Calculation:

Sample size was calculated using G*Power version 3.1. Based on a pilot study of 10 patients per group, where the mean diaphragmatic excursion at 30 minutes was 1.85±0.29cm in the 0.02mg/kg neostigmine group and 2.09±0.37cm in the 0.04mg/kg group. Assuming a power of 80% and alpha error of 0.05, the estimated sample size required to detect this difference was 25 patients per group.

Statistical analysis:

Statistical analysis was performed using IBM SPSS Statistics version 26.0. Continuous data are presented as mean±SD (if normally distributed) or median (IQR) (if non-normal). Between-group comparisons use independent-samples *t*-test or Mann–Whitney *U* test as indicated, and within group comparisons use repeated-measures ANOVA. Categorical variables were summarized as counts and percentages and compared using the Chi-square test or Fisher's exact test. A two-sided *p*-value of <0.05 was considered statistically significant.

RESULTS

A total of 60 patients scheduled for elective laparoscopic cholecystectomy under general anesthesia were screened for eligibility. Ten patients were excluded — six due to protocol violations (such as BMI >35kg/m² or pulmonary disease) and four who declined participation. The remaining 50 eligible patients were randomized into two groups:

- Group F (full-dose neostigmine, 0.08mg/kg), *n*= 25
- Group H (half-dose neostigmine, 0.04mg/kg), *n*= 25

Fifty patients completed the study without dropout or protocol deviation. The trial's progress is summarized in the CONSORT diagram (Figure 1) and detailed in text format above.

Demographic and clinical profiles were well-balanced between groups (Table 1). There were no statistically significant differences in age, sex distribution, BMI, ASA classification, or comorbidities, confirming successful randomization (*p*>0.05 for all comparisons).

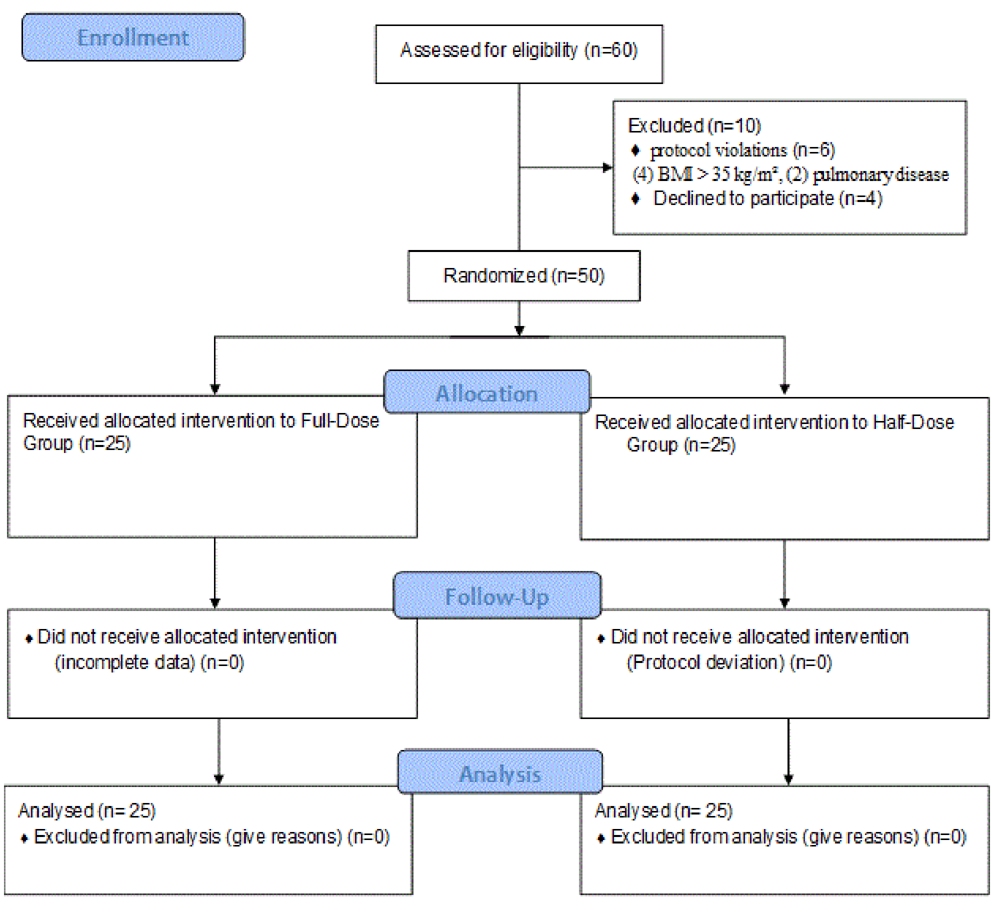

Fig. 1: CONSORT Flow Chart.

Table 1: Distribution of patients' characteristics between the studied groups:

	Full dose (*n*= 25)	Half dose (*n*= 25)	*P*-value
Age/years (Mean±SD)	38.28±9.3	38.84±10.5	0.834*
BMI (kg/m²) (Mean±SD)	32.33±1.3	32.73±1.4	0.297*
Sex			
Male	6(24%)	7(28%)	0.747**
Female	19(76%)	18(72%)	
Comorbidities			
DM	8(32%)	9(36%)	0.765**
HTN	7(28%)	8(32%)	0.758**
IHD	0(0%)	1(4%)	0.312**
ASA status			
I	16(64%)	13(52%)	0.390**
II	9(36%)	12(48%)	

Independent Sample *T*-test; Chi-square test or Fisher's exact test; SD: Standard deviation; BMI: Body Mass Index; DM: Diabetes Mellitus; HTN: Hypertension; IHD: Ischemic Heart Disease; ASA: American Society of Anesthesiologists; *P* value >0.05: Not significant; *P* value <0.05 is statistically significant.

Both groups exhibited a statistically significant decline in DE at all postoperative time points (0-, 10-and 30-minutes post-reversal) compared to pre-induction baseline ($p<0.001$ within groups). Mean DE values at 30 minutes post reversal were in Group F: 1.43±0.3cm vs. 1.34±0.3cm in group H. There were no significant differences between the groups at any time point ($p= 0.757$ at 30min post reversal), suggesting that diaphragmatic mobility recovered similarly regardless of neostigmine dose (Figure 2; Table 2).

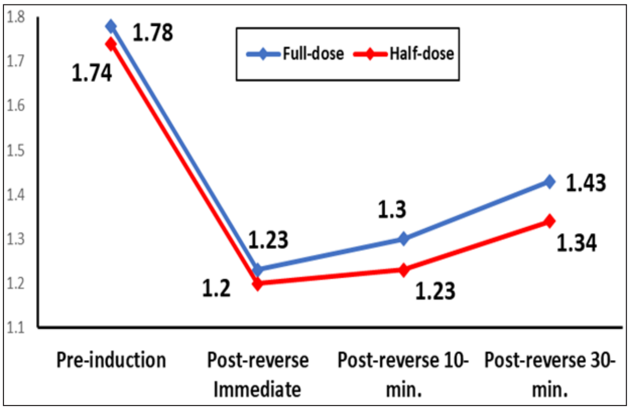

Fig. 2: Distribution of Diaphragmatic excursion between groups.

Table 2: Distribution of Diaphragmatic excursion between the studied groups:

	Full dose *N*= 25	Half dose *N*= 25	*P*-value*
Pre induction Mean±SD	1.78±0.1	1.74±0.1	0.360
Post reverse immediately Mean±SD	1.23±0.2	1.20±0.4	0.399
Post reverse 10 mins Mean±SD	1.30±0.3	1.23±0.2	0.343
Post reverse 30 mins Mean±SD	1.43±0.3	1.43±0.3	0.757
p-value**	< 0.001	<0.001	

Two-way RM ANOVA; *: between groups; **: within group; SD: Standard deviation; *P* value >0.05: Not significant; *P* value <0.05 is statistically significant; $p<0.001$ is highly significant.

DTF also declined significantly in both groups after reversal ($p<0.001$ within groups). Mean DTF at 30 minutes post-reversal were in Group F: 50.53±2.8% vs. 49.52±7.1% in Group H. Intergroup comparisons at all time points showed no statistically significant differences ($p= 0.089$ at 30min), indicating equivalent contractile function recovery across dosing strategies (Table 3; Figure 3).

Table 3: Distribution of Diaphragmatic Thickening Fraction between groups:

Mean±SD	Full dose *N*= 25	Half dose *N*= 25	*P*-value*
Pre induction (%)	53.09±4.9	52.60±3.9	0.689
Post reverse immediately (%)	49.26±4.4	46.98±4.9	0.506
Post reverse 10 mins (%)	50.09±4.3	47.93±5.1	0.111
Post reverse 30 mins (%)	50.53±2.8	49.52±7.1	0.089
P-value**	0.032	<0.001	

Two-way RM ANOVA; **: within group; *: between groups; SD: Standard deviation; *P* value >0.05: Not significant; *P* value <0.05 is statistically significant; $p<0.001$ is highly significant.

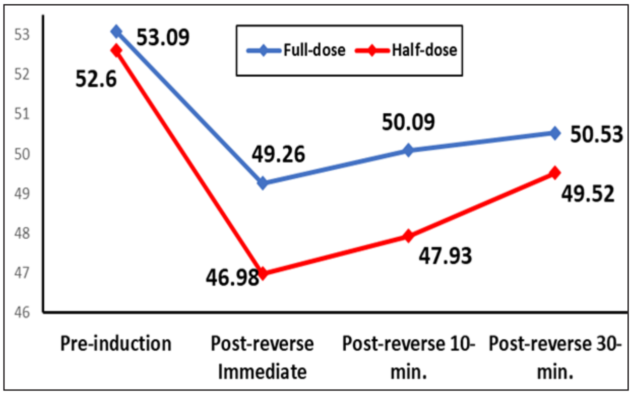

Fig. 3: Distribution of Diaphragmatic Thickening Fraction between groups.

Heart rate, mean arterial pressure (MAP), and SpO_2 remained within normal clinical limits and did not differ significantly between groups at any measured interval. No patients required pharmacologic intervention for hemodynamic instability.

ABG values obtained 30 minutes post-reversal demonstrated no significant intergroup differences: PaO_2, $PaCO_2$, and pH values were similar, confirming adequate ventilation and gas exchange under both dosing regimens.

The full-dose neostigmine group experienced a significantly higher incidence of muscarinic side effects Vomiting: 48% (Group F) vs. 16% (Group H); $p= 0.015$, Bradycardia: 40% (Group F) vs. 12% (Group H); $p= 0.024$, Excessive salivation: 48% (Group F) vs. 20% (Group H); $p= 0.037$, Nausea occurred in both groups (52% in Group F vs. 40% in Group H), but this difference was not statistically significant ($p= 0.395$) (Table 4).

These findings highlight the clinical benefit of dose reduction in minimizing cholinergic complications without compromising efficacy.

The mean PACU stay was in Group F: 38.04±6.4 minutes vs. 38.92±7.8 minutes in Group H. No statistically significant difference was noted ($p= 0.953$), indicating that lower neostigmine dosing does not delay discharge readiness.

Table 4: Distribution of Complications and outcomes between groups:

	Full dose **N= 25**	**Half dose** **N= 25**	***P*-value**
Complications			
Nausea	13(52%)	10(40%)	0.395*
Vomiting	12(48%)	4(16%)	0.015*
Bradycardia	10(40%)	3(12%)	0.024*
Salivation	12(48%)	5(20%)	0.037*
PACU (Mean ± SD)	38.04±6.4	38.92±7.8	0.953**

*: Chi-square test was used to compare Difference in Frequency between Groups; **: Independent Sample *T*-test was used to compare Difference in Mean between Groups; SD: Standard deviation; P value >0.05: Not significant; P value <0.05 is statistically significant; p<0.001 is highly significant.

DISCUSSION

This randomized controlled trial compared two neostigmine dosing strategies—full dose (0.08mg/kg) versus half dose (0.04mg/kg)—for reversing residual neuromuscular blockade (RNMB) in patients undergoing laparoscopic cholecystectomy. Diaphragmatic recovery was assessed using ultrasound-based metrics: diaphragmatic excursion (DE) and diaphragmatic thickening fraction (DTF). Our findings demonstrate that both dosing regimens yielded equivalent recovery of diaphragmatic function, while the half-dose strategy significantly reduced cholinergic side effects such as bradycardia, salivation, and vomiting.

These results contribute to a growing body of evidence supporting a more individualized and nuanced approach to neostigmine dosing. Traditionally, neostigmine has been administered in doses ranging from 0.04 to 0.08mg/kg based on clinical judgment and the depth of neuromuscular blockade[7]. However, recent literature suggests that lower doses may be sufficient when reversal is initiated after spontaneous recovery has begun, particularly at a TOF count ≥2[10,17]. In this study, both groups received reversal at that threshold, which likely contributed to the comparable efficacy of the lower dose.

Unlike many studies that focus solely on peripheral muscle groups, this trial assessed diaphragmatic recovery directly—an organ of primary clinical importance for ventilation. The use of bedside ultrasonography to measure DE and DTF offers a functional and non-invasive evaluation of respiratory muscle performance, validated in both perioperative and critical care settings[14,15]. The significant postoperative decline in DE and DTF observed in both groups reflects the well-established impact of laparoscopy and anesthesia on diaphragmatic dynamics[4,5]. However, the absence of intergroup differences suggests that a reduced neostigmine dose does not compromise diaphragm-specific recovery.

The significantly higher incidence of muscarinic side effects in the full-dose group aligns with previous pharmacologic understanding of neostigmine's mechanism of action. Increased acetylcholine availability affects both nicotinic and muscarinic receptors, leading to bradycardia, salivation, and gastrointestinal symptoms[8,9]. These side effects, although not life-threatening in healthy patients, can cause discomfort, prolong PACU monitoring, and may be poorly tolerated in higher-risk populations. The present findings support prior work suggesting that adverse effects are dose-dependent and may be mitigated by reducing the neostigmine dose without compromising efficacy[6,16].

Importantly, both dosing regimens maintained hemodynamic stability and effective ventilation, as reflected in unchanged ABG parameters, MAP, and SpO_2. These findings reinforce the safety of lower-dose neostigmine in low-risk patients when combined with anticholinergic agents like atropine[2]. Moreover, PACU discharge times were unaffected by dose reduction, confirming that lower doses do not prolong recovery in this population.

Our findings have direct implications for perioperative practice. They support the adoption of monitoring-guided, reduced-dose neostigmine reversal protocols in healthy patients with partial spontaneous recovery. Such an approach may enhance patient comfort, reduce drug-related side effects, and promote faster turnover in resource-limited PACU settings.

Although ultrasound identified a statistically significant reduction in DE and DTF from baseline in both study arms, clinical respiratory indices (ABG, SpO_2, MAP) and PACU discharge readiness remained within acceptable limits in this low-risk cohort. Thus, the reduction appears largely subclinical in healthy patients but may be consequential in higher-risk patients. Our findings therefore indicate that reversal with neostigmine at either dose—when given after TOF count ≥2—supports near-term ventilatory adequacy in ASA I–II patients but may not fully restore preoperative diaphragm metrics within 30 minutes. Studies powered for clinical outcomes (PPCs, oxygen dependency, reintubation) are needed to determine the clinical relevance of these early ultrasound changes[13].

While the study was adequately powered and methodologically sound, several limitations should be acknowledged: Population homogeneity: Our cohort consisted of ASA I–II adults (age 18–60) undergoing elective laparoscopic cholecystectomy; therefore, the results may not be generalizable to elderly patients, those with morbid obesity, or patients with significant cardiopulmonary disease who are at higher baseline risk for PPCs. Future studies should evaluate diaphragmatic recovery and clinical outcomes (PPCs, oxygen requirements, re-intubation) after different reversal strategies in these higher-risk groups. TOF site limitation: Peripheral TOF monitoring at the adductor pollicis does not necessarily reflect diaphragmatic recovery kinetics; although we measured diaphragmatic function directly by ultrasound, we did not correlate TOF indices with ultrasound measures in this study. Future research should directly evaluate correlations between peripheral TOF, diaphragm ultrasound, and patient-centered respiratory outcomes. Although no significant differences in diaphragmatic function were found between the two neostigmine dosing groups, both showed a significant decline from preoperative to postoperative measurements. This suggests that residual neuromuscular blockade may transiently impair diaphragmatic performance, even when TOF criteria are met. While Sugammadex rapidly and predictably reverses aminosteroid neuromuscular blockade and has been associated with more complete recovery in some studies; however, its availability and higher cost limit routine use in many hospitals worldwide. Thus, optimizing acetylcholinesterase inhibitor dosing (neostigmine) remains a practical priority in resource-limited settings, while randomized comparisons of diaphragmatic recovery using sugammadex vs neostigmine (particularly in high-risk patients) are warranted[17]. Lastly, this study did not evaluate long-term respiratory outcomes or postoperative pulmonary complications (PPCs). Future research should include extended follow-up to evaluate the clinical implications of improved early diaphragmatic recovery.

CONCLUSIONS

This randomized trial shows that a reduced neostigmine dose (0.04mg/kg) is as effective as the standard dose (0.08mg/kg) in restoring diaphragmatic function after laparoscopic cholecystectomy when given at a TOF count ≥2. Ultrasound assessments confirmed similar diaphragmatic recovery in both groups, while the lower dose significantly reduced cholinergic side effects without delaying recovery. These results support individualized, monitoring-guided dosing in low-risk patients. Our findings support that higher dose of neostigmine may enhance early diaphragmatic recovery; however, larger studies across varied populations are needed to guide individualized dosing strategies.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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