SUGAMMADEX VERSUS NEOSTIGMINE FOR REVERSAL OF NEUROMUSCULAR BLOCKADE AND PREVENTION OF RESPIRATORY ADVERSE EVENTS FOLLOWING FUNCTIONAL ENDOSCOPIC SINUS SURGERY: A RANDOMIZED DOUBLE-BLIND STUDY

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Abstract

Objective

To compare perioperative respiratory adverse events (PRAEs) and neuromuscular recovery following reversal of vecuronium-induced neuromuscular blockade with sugammadex versus neostigmine in patients undergoing functional endoscopic sinus surgery (FESS).

Methods

In this prospective randomized double-blind study, 70 ASA I–II patients undergoing FESS were allocated to receive either sugammadex 4 mg/kg (Group A) or neostigmine 0.05 mg/kg with glycopyrrolate 0.4 mg (Group B). Neuromuscular function was monitored using train-of-four (TOF). The primary outcome was incidence of PRAEs. Secondary outcomes included time to TOF recovery, haemodynamics, and recovery profile.

Results

PRAEs were significantly lower in Group A (17.1%) compared with Group B (74.3%) ($p < 0.001$). Bucking and straining were significantly higher in Group B ($p < 0.001$). Time to TOF recovery was significantly shorter with sugammadex (122.14 ± 56.82 s vs 465.71 ± 113.05 s; $p < 0.001$). Haemodynamic variables were comparable between groups.

Conclusion

Sugammadex provides faster neuromuscular recovery and significantly reduces early PRAEs compared with neostigmine in Functional endoscopic sinus surgery patients.

Keywords: Sugammadex, Neostigmine, Neuromuscular Blockade, Neuromuscular Monitoring, Train-of-Four Monitoring

1. Introduction

Functional endoscopic sinus surgery (FESS) stands as the gold standard for managing chronic rhinosinusitis and other complex sinonasal conditions that do not respond to conservative medical therapies [1,2]. While modern endoscopic equipment and refined surgical methodologies have made it easier to restore natural sinus ventilation and mucociliary clearance with minimal tissue trauma, the procedure presents a unique set of challenges for the anaesthesia provider [1,2]. Because surgeons and anaesthetists must share a highly vascular, narrow airway, patients face specific intraoperative risks. Managing controlled hypotension is frequently required to maintain surgical visibility, and the presence of postoperative nasal packing, blood pooling, and fluid contamination significantly threatens upper airway patency during the emergence phase of anaesthesia [3].

To ensure stable operating conditions, facilitate smooth endotracheal intubation, and prevent sudden patient movement near delicate facial structures, clinicians routinely utilize neuromuscular blocking agents. However, ensuring a complete return of muscle function before extubation remains an ongoing clinical challenge. Postoperative residual neuromuscular blockade (RNMB)—objectively defined as a train-of-four (TOF) ratio below 0.9 when measured at the adductor pollicis frequently persists into early recovery [4]. At this level of subtle paralysis, upper airway tone and protective airway reflexes are fundamentally compromised [4]. Despite the widespread, routine administration of pharmacological reversal agents, contemporary literature reveals that RNMB still affects between 19% and 64% of patients arriving at the post-anaesthesia care unit [4,5].

The clinical implications of even mild residual paralysis are deeply concerning. Incomplete reversal impairs pharyngeal muscle tone, disrupts swallowing coordination, and blunts normal ventilatory responses to hypoxia. This directly increases the likelihood of severe perioperative respiratory adverse events (PRAEs), including acute hypoxemia, physical airway obstruction, laryngospasm, silent aspiration, and the need for emergency reintubation [6]. For patients undergoing FESS, these systemic risks are compounded by localized anatomical factors, such as preexisting nasal obstruction, surgical trauma, mucosal edema, and blood accumulation in the hypopharynx.

Historically, the acetylcholinesterase inhibitor neostigmine has served as the standard choice for reversing non-depolarizing muscle relaxants. Yet, neostigmine features inherent limitations; its efficacy drops sharply during deep blockade, and its mechanism triggers systemic muscarinic side effects that require co-administration with anticholinergic drugs. Conversely, sugammadex offers a different pharmacological approach as a selective relaxant binding agent. By encapsulating steroidal neuromuscular blockers like vecuronium or rocuronium directly, it delivers rapid, predictable reversal independent of the acetylcholine pathway, significantly lowering the baseline incidence of both residual paralysis and subsequent respiratory complications [7,8].

While the broad pharmacological superiority of sugammadex over neostigmine is well-documented in general surgery, targeted data focusing explicitly on the high-risk FESS population remains surprisingly sparse. Given the acute airway vulnerabilities inherent to sinus surgeries and the modern shift toward rapid-track outpatient care, identifying the most effective strategy to minimize PRAEs is a matter of clear clinical urgency [9]. Accordingly, the current study was designed to evaluate and compare the incidence of perioperative respiratory adverse events following neuromuscular blockade reversal with either sugammadex or neostigmine in patients undergoing functional endoscopic sinus surgery.

2. Materials And Methods

Study Design and Setting

This prospective, randomized, double-blind clinical trial was carried out within the Department of Anaesthesiology at the Sri Guru Ram Das Institute of Medical Sciences and Research, located in Sri Amritsar, Punjab, India. The investigation spanned from July 2024 to December 2025. Prior to commencement, the study protocol received formal clearance from the Institutional Research and Ethics Committee under reference numbers SGRD/IEC/2024-313 and CTRI/2024/11/076218. All prospective

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participants provided written, informed consent before being enrolled in the trial.

Sample size calculations were grounded in data from prior literature [10], which indicated an anticipated variance of roughly 40% in the rate of PRAEs between the study groups. Setting the type I error rate (α) at 0.05 and the statistical power at 80%, the minimum cohort size was determined to be 32 participants per arm. To safeguard the validity of the data against potential patient attrition or dropouts, a total of 35 participants were allocated to each cohort.

Study Population and Selection Criteria

The study evaluated adult patients aged between 18 and 75 years, classified under the American Society of Anaesthesiologists (ASA) physical status I or II, who were booked for elective functional endoscopic sinus surgery (FESS) under general anaesthesia.

Inclusion Criteria: Patients aged 18-75 years, designated as ASA physical status I-II, scheduled for an elective FESS procedure.

Exclusion Criteria: Individuals with a recognized allergy or hypersensitivity to the investigational drugs; a documented history of chronic respiratory pathology or an active respiratory tract infection; a history of substance abuse or tobacco smoking; and individuals exhibiting renal impairment with serum creatinine levels exceeding 1.5 mg/dL.

Randomization and Blinding Protocols

Enrolled participants were assigned to one of two arms using an automated, computer-generated randomization sequence. To protect allocation concealment, sequentially numbered, sealed opaque envelopes were utilized and opened only immediately before medication preparation. The anaesthesiologist tasked with preparing the study drugs was entirely insulated from subsequent patient care and data collection. This separation of duties successfully maintained double-blinding for both the primary investigator and the outcome assessor.

Investigational Groups

Group S (Sugammadex Arm): Participants received an intravenous bolus of sugammadex at a dose of 4 mg/kg to reverse neuromuscular blockade.

Group N (Neostigmine Arm): Participants received an intravenous injection containing a mixture of neostigmine 0.05 mg/kg and glycopyrrolate 0.4 mg for pharmacological reversal.

Anaesthetic Protocol

A uniform anaesthetic workflow was applied across all study participants. Preoperative fasting intervals adhered strictly to established guidelines, requiring a 6-hour restriction for solid foods and a 2-hour window for clear fluids. Premedication consisted of oral alprazolam 0.25 mg, administered both the night preceding surgery and on the morning of the operation.

Upon arrival in the operating room, standard non-invasive monitors were applied, including five-lead electrocardiography, pulse oximetry, and non-invasive blood pressure (NIBP) measurement to establish baseline hemodynamic values. Prior to the induction of anaesthesia, patients received intravenous glycopyrrolate 0.01 mg/kg and butorphanol 0.02 mg/kg.

Following a 3-to-5-minute period of preoxygenation with 100% oxygen, general anaesthesia was induced via intravenous propofol 2 mg/kg. Once adequate face-mask ventilation was confirmed, succinylcholine 2 mg/kg was administered to facilitate smooth endotracheal intubation. After securing the airway with a properly sized, cuffed endotracheal tube, maintenance of neuromuscular blockade was achieved using vecuronium 0.04 mg/kg.

Anaesthesia maintenance relied on titrated isoflurane (1-2%) delivered in a carrier gas mixture of 60% nitrous oxide and 40% oxygen. Continuous intraoperative tracking monitored heart rate, arterial blood pressure, SpO_2, end-tidal carbon dioxide ($EtCO_2$), and fractional inspiratory/expiratory oxygen concentrations. Mechanical ventilation parameters were adjusted dynamically to ensure normocapnia, targeting an $EtCO_2$ range between 30 and 40 mmHg. Anaesthetic depth was titrated to maintain a minimum alveolar concentration (MAC) between 1 and 1.5. Additionally, a dexmedetomidine infusion

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was initiated with an initial loading dose of 1 μg/kg delivered over 10 minutes, followed by a continuous maintenance rate of 0.5 μg/kg/h.

Intraoperative Maintenance and Neuromuscular Tracking

Objective neuromuscular monitoring via train-of-four (TOF) stimulation was deployed for every participant. Approximately 30 minutes before the anticipated conclusion of the surgery, prophylactic antiemetic and analgesic therapies were administered, consisting of intravenous ondansetron 4 mg and paracetamol 1.0g. The dexmedetomidine infusion was terminated exactly 15 minutes before the completion of the surgical procedure.

At the end of the operation, the inhalational anaesthetic agent was turned off, and fresh gas flow was adjusted upward to 6 L/min. Pharmacological reversal was initiated only after the participant exhibited a TOF count of 2 or greater. Extubation was deferred until objective monitoring demonstrated a TOF ratio of 0.9 or greater, alongside corroborating clinical indicators of recovery. The precise time interval required for the TOF ratio to recover from 0.2 up to 0.9 was tracked and documented for both cohorts.

Assessment of Outcomes

The primary focus of this study was to evaluate the rate of perioperative respiratory adverse events (PRAEs). A PRAE was defined by the clinical presentation of any of the following signs during the emergence phase or within the immediate postoperative window: laryngospasm, coughing, bucking, respiratory straining, or oxygen desaturation (noted as an SpO_2 less than 90% while breathing room air).

Laryngospasm severity was systematically graded using a four-point instrument:

- 0 = No evidence of laryngospasm
- 1 = Presence of inspiratory stridor
- 2 = Complete closure of the vocal cords
- 3 = Development of cyanosis

For the purposes of statistical analysis, any recorded grade of laryngospasm (grades 1, 2, or 3) was classified as a clinically significant PRAE. Similarly, coughing severity was tracked using a 0-to-4 grading scale; however, only severe presentations (categorized as grades 3 and 4) were deemed clinically significant and included in the final PRAE datasets.

Secondary endpoints included intraoperative and postoperative hemodynamic fluctuations, the exact timeline of neuromuscular recovery, and the incidence of postoperative complications. These complications included bradycardia, tachycardia, hypotension, respiratory depression, nausea, and vomiting.

Postoperative Care and Monitoring

Following successful extubation, participants were relocated to the post-anaesthesia care unit (PACU), where their recovery status was quantified using the Modified Aldrete Score. Routine supportive medical care was provided, and clinicians continuously observed the patients for any emergent cardiorespiratory or neurological variations.

Management Protocol for Adverse Events

Hypotension: Defined as a reduction in systolic blood pressure exceeding 20% of the baseline value; managed with an intravenous crystalloid fluid challenge (normal saline at 10 mL/kg) and titrated boluses of mephentermine 6 mg.

Hypertension: Defined as an increase in systolic blood pressure exceeding 20% of the baseline value; addressed with targeted medical therapy based on clinical judgment.

Bradycardia: Defined as a heart rate dropping below 60 beats/min or a reduction greater than 20% from baseline; treated via an intravenous injection of atropine 0.6 mg.

Tachycardia: Defined as a heart rate elevation exceeding 20% of baseline values; managed according to standard clinical algorithms.

Postoperative Nausea and Vomiting (PONV): Managed with rescue doses of intravenous ondansetron 4 mg.

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Respiratory Depression: Defined as a respiratory rate falling below 10 breaths per minute; addressed immediately with targeted ventilatory assistance.

Statistical Analysis

Collected data were organized, tabulated, and analysed using SPSS software, version 26.0 (IBM Corp., Armonk, NY, USA). Continuous clinical variables were expressed as mean values ± standard deviation. Categorical datasets were quantified as absolute frequencies and corresponding percentages. Intergroup statistical analysis for continuous data was performed utilizing the independent Student's t-test, whereas categorical datasets were cross-compared using the Chi-square test. Statistical significance was established at a p-value less than 0.05, and highly significant differences were defined by a p-value less than 0.001.

3. Results

A total of 70 patients undergoing functional endoscopic sinus surgery were enrolled and randomized equally into two groups: Group A (sugammadex, n=35) and Group B (neostigmine, n=35). All patients completed the study and were included in the final analysis (Figure 1: CONSORT flow diagram).

Baseline Demographic and Clinical Characteristics

Both groups were comparable with respect to demographic variables and baseline clinical characteristics. The mean age was 40.43±11.65 years in Group A and 35.83 ± 10.59 years in Group B, with no statistically significant difference between groups ($p = 0.088$). Gender distribution was also comparable, with males predominating in both groups (71.4% vs. 68.6%, $p = 0.794$, Table 1). Similarly, ASA physical status distribution showed no intergroup difference ($p = 0.788$). The mean body mass index (BMI) was 27.63 ± 2.43 kg/m² in Group A and 27.48 ± 2.78 kg/m² in Group B, which was statistically comparable (p=0.819, Table 1).

Table 1. Baseline Demographic and Clinical Characteristics

Variable	Group A (Sugammadex) (n=35)	Group B (Neostigmine) (n=35)	p value
Age (years, mean ± SD)	40.43 ± 11.65	35.83 ± 10.59	0.088
BMI (kg/m², mean ± SD)	27.63 ± 2.43	27.48 ± 2.78	0.819
Male, n (%)	25 (71.4%)	24 (68.6%)	0.794
Female, n (%)	10 (28.6%)	11 (31.4%)	—
ASA I, n (%)	25 (71.4%)	26 (74.3%)	0.788
ASA II, n (%)	10 (28.6%)	9 (25.7%)	—

Primary Outcome: Perioperative Respiratory Adverse Events (PRAEs)

The table 2 analyses the distribution and specific manifestations of Perioperative Respiratory Adverse Events (PRAEs) between Group A and Group B (n=35 each). A striking disparity is evident: 74.3% of Group B patients suffered at least one PRAE, whereas 82.9% of Group A remained completely unaffected (($\chi^2 = 23.14$, $p < 0.001$).

Granular analysis reveals that this gap is driven primarily by bucking (57.1% vs. 5.7%) and straining (51.4% vs. 8.6%), both showing highly significant elevations in Group B ($p < 0.001$). Conversely, variations in laryngospasm, coughing, and desaturation rates did not reach statistical significance ($p > 0.05$).

Table 2. Overall Incidence of Perioperative Respiratory Adverse Events (PRAEs)

Outcome	Group A (n=35)	Group B (n=35)	χ^2	p value
PRAEs present	6 (17.1%)	26 (74.3%)	23.14	<0.001*
No PRAEs	29 (82.9%)	9 (25.7%)	—	—
Components of Perioperative Respiratory Adverse Events				

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Laryngospasm	2 (5.7%)	5 (14.3%)	0.432
Coughing	1 (2.9%)	6 (17.1%)	0.102
Bucking	2 (5.7%)	20 (57.1%)	<0.001*
Straining	3 (8.6%)	18 (51.4%)	<0.001*
Desaturation (SpO_2 <90%)	1 (2.9%)	4 (11.4%)	0.356

*Significant; Chi-square test used for categorical variables.

Postoperative Recovery (Aldrete Score)

Recovery in the post-anaesthesia care unit was significantly faster in the sugammadex group.

At 10 minutes, a significantly higher proportion of patients in Group A achieved Aldrete score ≥9 compared to Group B (p=0.001). At 15 minutes, all patients in Group A had achieved adequate recovery, whereas 25.7% of Group B patients still had scores <9. By 30 minutes, all patients in both groups achieved satisfactory recovery (Table 3).

Table 3. Rapid Recovery of Neuromuscular and Functional Status

Parameter	**Group A (Sugammadex)**	**Group B (Neostigmine)**	**p value**
Time to TOF 0.2 → 0.9 (seconds)	122.14 ± 56.82	465.71 ± 113.05	<0.001*
Aldrete Score Recovery in PACU			
Time Point	**Group A ≥9**	**Group B ≥9**	**p value**
0 min	1 (2.9%)	0 (0%)	0.313
10 min	20 (57.1%)	7 (20.0%)	0.001*
15 min	35 (100%)	26 (74.3%)	0.001*
30 min	35 (100%)	35 (100%)	—

*Data expressed as mean ± SD for continuous variables and n (%) for categorical variables. Intergroup differences analyzed using the Independent Student's t-test (for TOF recovery time) and the Chi-square test / Fisher's exact test (for Aldrete scores). Statutory significance at $p < 0.05$.

The figure 1 illustrates the mean ± SD values of heart rate and mean arterial pressure from induction to 120 minutes postoperatively in both study groups. Both groups demonstrated a transient increase in HR and MAP during extubation, followed by a gradual decline during the postoperative period, with comparable haemodynamic profiles between the groups.

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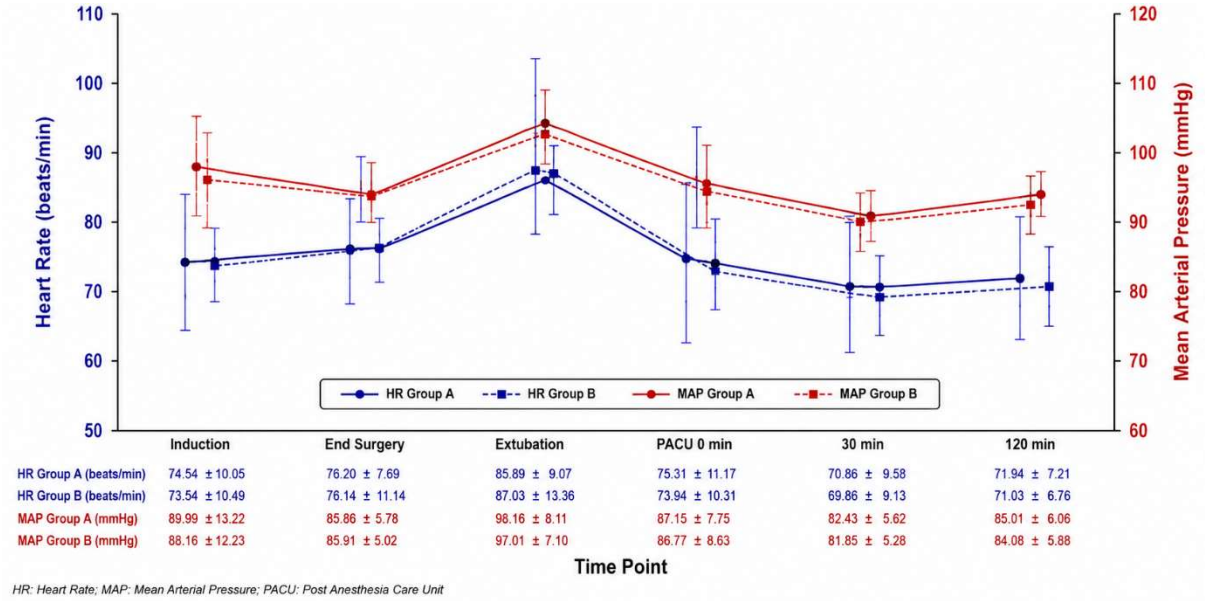

Figure 1: Changes in Heart Rate (HR) and Mean Arterial Pressure (MAP) at Different Perioperative Time Points in the Sugammadex (Group A) and Neostigmine (Group B) Groups

The table 4 tracks oxygen saturation (SpO_2) trends between Group A and Group B across six surgical intervals. Both cohorts maintained excellent, stable oxygenation profiles throughout the study. Intergroup differences remained statistically insignificant at all intervals ($p > 0.05$), with both groups safely recovering to baseline saturation levels by 120 minutes.

Table 4. Stable Perioperative Oxygenation Profile (SpO_2)

Time Point	Group A	Group B	p value
Induction	99.00 ± 1.50	98.94 ± 1.49	0.873
End Surgery	99.60 ± 0.91	99.63 ± 0.91	0.896
Extubation	97.89 ± 1.78	96.91 ± 2.79	0.087
PACU 0 min	97.49 ± 1.27	97.34 ± 1.28	0.641
30 min	97.86 ± 1.26	97.86 ± 1.22	0.999
120 min	98.09 ± 0.98	98.11 ± 0.90	0.899

*Data expressed as Mean ± SD; Student's t-test used for intergroup comparison.

The table 5 tracks postoperative complications between both groups (n=35 each). Minor occurrences of nausea, bradycardia, and hypotension showed no statistically significant differences ($p > 0.05$). Severe events like hypertension and respiratory depression were entirely absent, demonstrating a highly favorable, comparable safety profile for both cohorts.

Table 5. Comparison of Postoperative Adverse Events

Adverse Event	Group A (n=35)	Group B (n=35)	p value
Nausea/Vomiting	4 (11.4%)	7 (20.0%)	0.327
Bradycardia	2 (5.7%)	3 (8.6%)	0.643
Hypotension	1 (2.9%)	1 (2.9%)	0.754
Hypertension	0	0	—
Respiratory depression	0	0	—

*Data expressed as n(%). Intergroup differences analyzed using the Chi-square test (or Fisher's exact test for cell counts < 5). Statistical significance defined as $p < 0.05$.

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4. Discussion

The present study compared sugammadex and neostigmine for reversal of neuromuscular blockade in patients undergoing functional endoscopic sinus surgery (FESS), focusing on perioperative respiratory adverse events (PRAEs) and recovery profiles. The key finding was a significantly lower incidence of PRAEs in the sugammadex group (17.1%) compared with the neostigmine group (74.3%) Table 2, along with faster and more predictable neuromuscular recovery. These results underscore the clinical relevance of rapid reversal in shared-airway surgery, where even transient respiratory disturbances may compromise both patient safety and surgical conditions.

FESS is particularly susceptible to airway-related complications due to shared airway access, blood contamination, and emergence-related reflex stimulation. Residual neuromuscular blockade further exacerbates airway vulnerability by impairing pharyngeal muscle tone and protective reflexes. In this context, the markedly reduced PRAEs observed with sugammadex likely reflect more complete and rapid restoration of neuromuscular function.

Our findings align with Kheterpal et al.[11] demonstrated a 30% reduction in major pulmonary complications with sugammadex compared with neostigmine across a large surgical cohort, including lower rates of pneumonia and respiratory failure (4.8% vs. 3.5%). Similarly, Wang et al.[12] reported significantly reduced early respiratory adverse events and desaturation with sugammadex in a meta-analysis of randomized trials. Although these studies included heterogeneous populations, they consistently support improved respiratory safety with sugammadex.

In the present study, bucking and straining were significantly higher with neostigmine ($p< 0.001$, Table 2), highlighting inadequate synchronisation between recovery of airway reflexes and neuromuscular function. Such events are clinically important in FESS, as they may increase venous pressure and contribute to postoperative bleeding. Sugammadex, by providing rapid and predictable reversal, likely facilitates smoother emergence.

Laryngospasm and desaturation were numerically lower in the sugammadex group but not statistically significant. This is consistent with previous studies showing low absolute event rates and limited power to detect differences in rare airway complications. Al-alami et al. [13] also reported comparable laryngospasm rates between reversal agents (6.9% vs. 8.1%) in paediatric airway surgery, suggesting that extubation technique and depth of anaesthesia may be more influential than the reversal drug itself.

Neuromuscular recovery was significantly faster with sugammadex (122.14±56.82 s vs. 465.71±113.05 s; $p<0.001$, Table 3), consistent with earlier randomized trials and meta-analyses demonstrating rapid reversal within minutes compared with delayed recovery using neostigmine [14-15]. However, despite this pharmacological advantage, modified Aldrete scores were comparable between groups, supporting previous observations that global recovery scales may lack sensitivity to detect subtle neuromuscular differences once discharge criteria are met [16].

Haemodynamic parameters remained stable and comparable between groups (Figure 1, Table 4), while oxygen saturation was slightly better in the sugammadex group during early recovery, consistent with prior evidence showing improved oxygenation without major haemodynamic differences [10,17].

Overall, this study demonstrates that sugammadex provides superior early respiratory safety and faster neuromuscular recovery in FESS, although haemodynamic stability and global recovery scores remain similar between agents. The findings support the preferential use of sugammadex in shared-airway procedures where rapid and complete recovery is essential. The findings of the present study have important implications for anaesthetic practice in shared-airway surgeries. By reducing emergence-related respiratory complications and facilitating rapid neuromuscular recovery, sugammadex may improve perioperative airway safety, optimize recovery room turnover, and potentially enhance patient satisfaction and surgical outcomes in FESS procedures.

Limitations

Several study limitations require acknowledgment. First, the single-center design and modest cohort size

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may constrain the external validity of our findings across broader surgical populations. Second, the exclusive enrolment of ASA physical status I–II patients precludes direct extrapolation to high-risk cohorts with severe cardiopulmonary comorbidities. Third, postoperative surveillance was restricted to the immediate recovery phase, leaving delayed respiratory adverse events, total hospital duration, and long-term outcomes unexamined. Additionally, objective quantitative evaluations of diaphragmatic and pulmonary function were not performed. Finally, while sugammadex demonstrated superior clinical efficacy, a formal pharmacoeconomic analysis was omitted, which represents a critical determinant for routine adoption in resource-limited clinical settings.

5. Conclusion

Sugammadex demonstrated superior clinical efficacy over neostigmine by facilitating significantly accelerated and more predictable reversal of vecuronium-induced neuromuscular blockade in patients undergoing functional endoscopic sinus surgery (FESS). This rapid recovery correlated with a pronounced reduction in perioperative respiratory adverse events, specifically mitigating emergence bucking and straining, which enhanced airway safety and optimized the recovery profile. While intraoperative hemodynamic stability and overall postoperative discharge scores remained comparable between the cohorts, the marked reduction in respiratory complications highlights the clinical utility of sugammadex. Consequently, these findings support its preferential administration in shared-airway interventions like FESS, where the prompt reinstatement of protective airway reflexes and respiratory function is paramount.

Declarations

Ethical Approval and Consent to Participate

All clinical protocols executed within this investigation strictly adhered to the ethical principles mandated by the institutional research board and the 1964 Declaration of Helsinki, including its subsequent revisions. Approval for this protocol was formally granted by the Institutional Ethics Committee (Ref No. SGRD/IEC/2024-313 and CTRI/2024/11/076218). Prior to any clinical intervention or data collection, prospective written informed consent was secured from every individual participant or their designated legal guardians.

Consent for Publication

Explicit written informed consent regarding the publication of clinical presentation details, demographic data, and associated diagnostic imagery was provided by the patients or their authorized legal representatives. To preserve subject confidentiality and privacy, all clinical parameters have been comprehensively de-identified and anonymized.

Availability of Data and Materials

The primary datasets compiled and evaluated throughout the course of this study are available from the corresponding author upon reasonable request, subject to institutional data governance frameworks and ethical sharing constraints.

Competing Interests

The authors declare that no financial, institutional, or professional conflicts of interest exist that could compromise or bias the presentation, interpretation, or objectivity of this research.

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Authors' Contributions

All individuals listed as authors contributed substantially to the initial conceptualization, methodological design, data acquisition, and statistical interpretation of this study. Every author was actively engaged in drafting the manuscript and executing critical revisions for refined intellectual content. The finalized manuscript has been collectively reviewed, verified, and approved by all authors prior to formal submission.

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