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OPTIMIZED REVERSAL WITHOUT TRAIN-OF-FOUR MONITORING VERSUS REVERSAL USING QUANTITATIVE TRAIN-OF-FOUR MONITORING: AN EQUIVALENCE STUDY

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Abstract

Background:
Neuromuscular blocking agents (NMBAs) such as atracurium and vecuronium are frequently used to facilitate intubation during general anesthesia, with residual paralysis posing potential morbidity risks postoperatively. Quantitative train-of-four (TOF) monitoring has shown promise in reducing residual paralysis, but its availability is limited. This study compares optimized reversal without TOF monitoring to reversal using quantitative TOF monitoring.

Methods:
We conducted a prospective randomized observational study in the Department of Anesthesiology at Saveetha Medical College & Hospital, enrolling 100 patients scheduled for elective surgeries under general anesthesia with NMBAs. Patients were stratified by surgery type and randomized into Group A (TOF monitoring-guided reversal) and Group B (optimized clinical reversal without TOF monitoring). The primary outcome was the incidence of residual paralysis (TOF ratio <0.90) in the recovery room.

Results:
Both groups were demographically comparable. Residual paralysis occurred in 4% of Group A and 10% of Group B. Other adverse events, including hypoxemia, reintubation, and nausea/vomiting, were infrequent and did not differ significantly between groups. Statistical analysis indicated that optimized reversal without TOF monitoring was not equivalent to TOF monitoring-guided reversal ($p<0.05$).

Conclusion:
Optimized clinical reversal without quantitative TOF monitoring does not provide equivalent protection against residual paralysis compared to TOF-based strategies. TOF monitoring should be preferred where available to reduce postoperative neuromuscular complications.

Keywords: Neuromuscular blocking agents, train-of-four monitoring, neostigmine, residual paralysis, anesthesia reversal.

INTRODUCTION

Atracurium and vecuronium are commonly used neuromuscular blocking agents (NMBAs) that facilitate tracheal intubation during general anesthesia. However, their use carries the risk of residual paralysis in the postoperative recovery room, occurring in an estimated 38-64% of cases with subjective or qualitative monitoring. Residual paralysis increases the incidence of airway obstruction, hypoxemia, pulmonary complications, and delayed discharge from the recovery area. Despite these risks, residual paralysis has not been universally recognized as a significant patient safety concern.

Quantitative train-of-four (TOF) monitoring, which objectively measures neuromuscular function, has been shown to reduce residual paralysis incidence. Nevertheless, the availability and routine use of quantitative TOF monitors remain limited, with reports indicating only 9.4-22.7% of clinicians consistently using them. In settings where TOF monitoring is unavailable, optimization of neostigmine reversal based on clinical signs and timing may enhance reversal success.

While evidence supports the benefit of TOF monitoring in guiding NMBA reversal, alternative strategies using optimized neostigmine administration without TOF guidance have not been thoroughly studied. This study aims to evaluate whether an optimized clinical reversal strategy without TOF monitoring is equivalent to a reversal strategy guided by quantitative TOF monitoring in preventing residual paralysis after atracurium and vecuronium administration. The findings seek to inform clinical practice in environments lacking access to neuromuscular monitoring devices.

MATERIALS AND METHODS

Study Design and Setting:
This prospective randomized observational study was conducted in the Department of Operation Theater and Anesthesia, Saveetha Medical College & Hospital from April 2024 to August 2024.

Study Population:
A total of 100 adult patients (>18 years) scheduled for elective surgeries under general anesthesia with intubation were enrolled. Patients were stratified and randomized into two equal groups (50 each).

Inclusion Criteria:
ASA physical status I and II, Age above 18 years, Undergoing elective surgery except head and neck surgery, General anesthesia using inhalational agents (isoflurane or sevoflurane) and Neuromuscular blocking agents (NMBAs): atracurium or vecuronium.

Exclusion Criteria:
Surgery duration less than 1 hour, Awake extubation or postoperative ICU admission, BMI less than 19 or greater than 35, Hepatic or renal insufficiency (creatinine >1.8 mg/dl), Contraindications to neostigmine or difficulties accessing TOF monitoring sites, History of hypersensitivity or allergy to anesthesia drugs

Randomization and Grouping:
Patients were randomized into two groups based on stratified randomization according to the surgery type:

- Group A: Reversal guided by quantitative train-of-four (TOF) monitoring
- Group B: Optimized clinical reversal without TOF monitoring

Anesthetic and Monitoring Protocol:
Standard anesthesia induction included intravenous midazolam (2 mg), propofol (1-2 mg/kg), fentanyl (100 μg), and rocuronium (0.6-0.8 mg/kg) for intubation. Maintenance anesthesia was provided with sevoflurane (1-3%) in an

oxygen-nitrous oxide mix (50:50). TOF-Watch SX device was used in Group A, with electrodes placed on the forearm stimulating the ulnar nerve and monitoring thumb movement.

Reversal Strategy:

- In Group A, neostigmine dosing was guided by the quantitative TOF ratio measured at the adductor pollicis. Neostigmine doses were adjusted based on TOF count and ratio levels, with dosing delayed if the TOF count was 0-1 and specific dosing tiers for TOF ratios ≤0.40, 0.40-0.70, and minimal block. Atropine sulfate 10 µg/kg IV was given with neostigmine.
- In Group B, reversal was optimized based on clinical signs such as spontaneous breathing and time elapsed since the last NMBA dose. Neostigmine doses were adjusted accordingly: 50 µg/kg IV if no spontaneous breathing after 30 minutes, 30-40 µg/kg with minimal spontaneous breathing, 20-30 µg/kg based on timing, and 10 µg/kg with adequate spontaneous breathing. Atropine was similarly administered.

Primary Outcome:
The incidence of residual paralysis in the recovery room, defined as a TOF ratio less than 0.90 at the adductor pollicis, measured twice by a blinded observer using the TOF-Watch SX acceleromyography device.

Additional Monitoring:
Oxygen saturation (SpO2), ECG, blood pressure, and respiratory status were monitored continuously. Adverse events such as hypoxemia, respiratory distress, reintubation, and postoperative nausea/vomiting were recorded.

Statistical Analysis:
Data were analyzed with SPSS 24. Continuous variables were compared using independent t-tests, and categorical data using Fisher's exact tests. Equivalence testing was conducted with a margin of 15%, 80% statistical power, and significance set at $p<0.05$.

RESULTS

Demographics:
Each group comprised 50 patients; groups matched for age, BMI, sex, ASA status.

Study Population and Baseline Characteristics

- Total patients: 100, equally randomized into two groups:
  - Group A (TOF monitoring): 50 patients
  - Group B (Optimized reversal without TOF monitoring): 50 patients
- Age:
  - Group A: Mean 40.14 ± 17.46 years
  - Group B: Mean 35.36 ± 11.29 years
  - p = 0.107 (not statistically significant)
- Sex distribution:
  - Group A: 48% male, 52% female
  - Group B: 46% male, 54% female
  - p = 0.841 (not statistically significant)
- Body Mass Index (BMI):
  - Group A: 24.51 ± 3.24 kg/m²
  - Group B: 24.11 ± 2.65 kg/m²
  - p = 0.503 (not statistically significant)
- ASA Physical Status:
  - Group A: 36% ASA I, 64% ASA II
  - Group B: 26% ASA I, 74% ASA II
  - p = 0.280 (not statistically significant)

Incidence of Residual Paralysis:

- Group A: 2/50 (4%)
- Group B: 5/50 (10%)

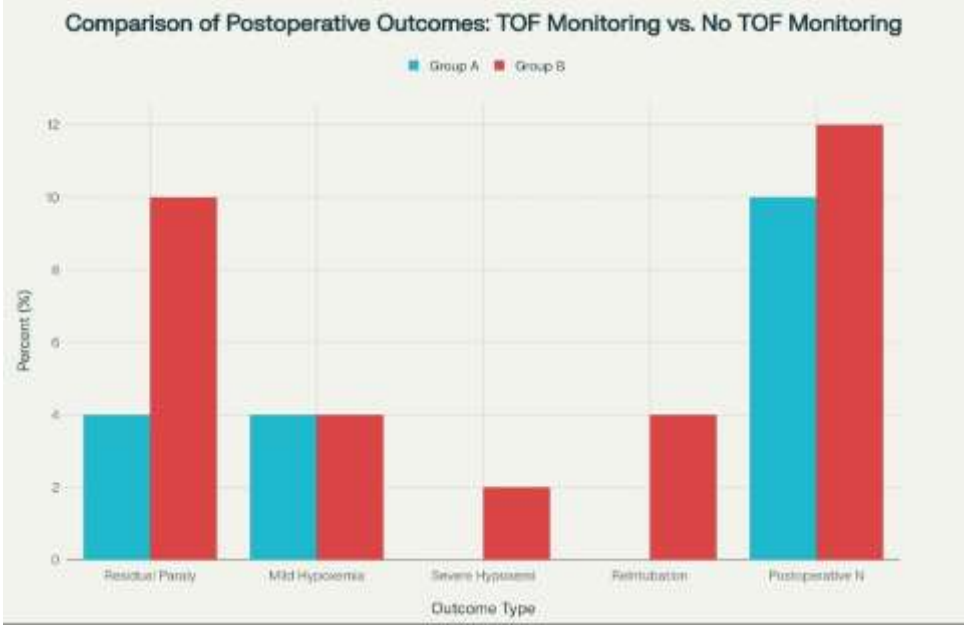
Difference was statistically significant and favored TOF monitoring.

Adverse Events:

- Mild hypoxemia: 4% in both groups
- Severe hypoxemia: 2% (Group B)
- Reintubation: 4% (Group B), 0% (Group A)
- Postoperative nausea/vomiting: 10% (Group A), 12% (Group B)

Other Observations:
No significant cardiac or respiratory distress observed; timing from reversal to extubation was longer in Group B

Parameter	**Group A**	**Group B**
Residual paralysis n(%)	2(4%)	5(10%)
Mild hypoxemia	2 (4%)	2 (4%)
Severe hypoxemia	0 (0%)	1 (2%)
Reintubation	0 (0%)	2 (4%)
Postoperative nausea/vomiting	5(10%)	6 (12%)



DISCUSSION

This study compared an optimized neostigmine reversal strategy without quantitative train-of-four (TOF) monitoring to TOF-guided reversal in patients receiving atracurium or vecuronium during general anesthesia. The results demonstrate that, although optimized, reversal without TOF monitoring was not equivalent to TOF-guided reversal in preventing residual paralysis.

Residual paralysis occurred in 10% of patients in the non-TOF group versus 4% in the TOF group. This aligns with previous evidence showing that objective neuromuscular monitoring reduces the incidence of residual blockade by ensuring appropriate dosing and timing of reversal agents. Absence of TOF data likely led to underestimation of blockade depth in the non-TOF group, contributing to higher paralysis rates.

Notably, severe respiratory events—including hypoxemia and reintubation—were only observed in the non-TOF group. This highlights the clinical importance of residual paralysis and supports the perioperative safety benefits of TOF monitoring.

Although the optimized clinical protocol in Group B incorporated time since last NMBA dose and visible clinical recovery, it was insufficient under inhalational anesthesia, which can prolong NMBA action. Extending reversal-to-extubation intervals toward 30 minutes may help reduce risk when monitoring is unavailable.

Limitations include the single-center setting, modest sample size, minor age differences between groups, lack of TOF ratio normalization, and potential temperature-related influences on TOF readings. Nevertheless, the findings reinforce existing guidelines recommending quantitative neuromuscular monitoring whenever possible.

Furthermore, our findings have important implications for patient safety and resource allocation in anesthesia practice. In many low- and middle-income settings, the availability of quantitative TOF monitoring remains limited due to cost, training gaps, or equipment constraints. This study highlights that, although optimizing neostigmine dosing based on clinical criteria and timing can reduce the risk of residual paralysis to some extent, it cannot fully replace objective monitoring. The higher incidence of residual paralysis and postoperative respiratory events in the non-TOF group reinforces international guidelines advocating routine neuromuscular monitoring for all patients receiving non-depolarizing muscle relaxants. Adoption of portable, cost-effective quantitative monitoring devices, coupled with staff training, could bridge this gap, improve recovery profiles, and potentially shorten postoperative stays by reducing reintubation and hypoxemia rates.

Clinical implications:

- TOF monitoring should be preferred when available.
- In resource-limited settings, cautious application of optimized protocols with prolonged observation is advisable.
- Future studies should explore extending reversal-extubation intervals and confirm whether normalized TOF ratios (>1.0) further improve safety.

CONCLUSION

An optimized clinical neostigmine reversal strategy without quantitative TOF monitoring was not equivalent to TOF-guided reversal in preventing postoperative residual paralysis after atracurium or vecuronium administration. Residual paralysis and serious respiratory events occurred more frequently when TOF monitoring was not used.

These findings support routine use of quantitative neuromuscular monitoring wherever available to enhance patient safety. In resource-limited settings without TOF devices, reversal protocols should be applied cautiously, with extended reversal-to-extubation intervals and vigilant postoperative observation to reduce complications.

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