Comparative Study of Neuromuscular Blocking Effects of Atracurium and Cisatracurium in Pediatric Patients Undergoing Elective Surgery Under General Anaesthesia

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ABSTRACT:

Background: Neuromuscular blocking agents (NMBAs) are integral part of pediatric anesthesia, in facilitating endotracheal intubation and providing muscle relaxation during surgery. Atracurium and Cisatracurium are commonly used non- depolarizing NMBAs, each with distinct pharmacological profiles. Aim of the study is to compare the neuromuscular blocking effects of Atracurium and Cisatracurium in pediatric patients undergoing elective surgery under general anaesthesia using neuromuscular monitoring [TOF].

Methods: Prospective, randomized controlled trial, 60 pediatric patients aged 1-12 years undergoing elective surgery under general anesthesia were randomly assigned to receive either Atracurium (0.5 mg/kg) or Cisatracurium (0.15 mg/kg) intravenously. Neuromuscular function was monitored using Train-of-Four (TOF). The primary outcomes measured were onset and duration of neuromuscular blocking effect using TOF monitor and quality of tracheal intubation. Secondary outcomes included were hemodynamic stability and the incidence of adverse effects.

Results: The research participants in both the groups had comparable characteristics with regards to demographic profile including the age, weight and gender distribution.The onset time for neuromuscular blockade was significantly faster with cisatracurium (2.6 ± 0.49 minutes) compared to atracurium (4.3 ± 0.46 minutes) ($p < 0.001$). The duration of neuromuscular blockade was significantly longer with cisatracurium (54.9 ± 3.2 minutes) than atracurium (27.8 ± 1.3 minutes) ($p < 0.001$). The time to recovery from neuromuscular blockade was significantly shorter with atracurium (27.4 ± 1.5 minutes) compared to cisatracurium (37.8 ± 1.1 minutes) ($p < 0.001$). Cisatracurium provided better intubating conditions, with a higher proportion of patients achieving excellent Cooper scores (90% vs. 66.7% for atracurium) ($p < 0.05$). Hemodynamic parameters and side effects were comparable between the two groups.

Conclusion: Both Atracurium and Cisatracurium are effective for neuromuscular blockade in pediatric patients. Cisatracurium had a quicker onset, longer duration of action, better intubating conditions and superior cardiovascular stability with minimal side effects although atracurium had a rapid recovery profile. Hence Cisatracurium is considered a preferable choice in pediatric patients for longer procedures or with cardiovascular concerns.

Keywords: Atracurium, Cisatracurium, pediatric anesthesia, neuromuscular blocking agents, elective surgery, intubation, Train-of-Four, hemodynamic stability.

Introduction:

Neuromuscular blocking agents (NMBAs) are essential in modern anesthesia practice, primarily used to facilitate endotracheal intubation and provide optimal surgical conditions by inducing muscle relaxation [1]. The evolution of NMBAs has significantly improved patient outcomes by enabling better control over muscle paralysis and minimizing side effects associated with older agents such as succinylcholine.

Atracurium and Cisatracurium are non-depolarizing NMBAs commonly used in paediatric anesthesia [1].

Atracurium, introduced in the 1980s, is most commonly used in paediatric patients as it has short half-life and independent metabolism which makes it an attractive option for renal and liver disease patients. Undergoes ester hydrolysis and spontaneous degradation by Hofmann elimination releasing Laudanosine and mono quartenary acrylate as metabolites which crosses the blood brain barrier and produces epileptogenic actions. Atracurium can cause histamine release, leading to potential side effects such as erythema, flush and bronchospasm [1, 2].

Cisatracurium, a 1R cis 1-'R stereoisomer of Atracurium, was introduced in United States in the year 1995. It has similar metabolism like atracurium but in contrary has no role in ester hydrolysis and does not release histamine [3]. The neuromuscular blocking efficacy of Cisatracurium is almost three times than that of Atracurium providing better cardiovascular stability and reduced side effects (4).

When equivalent doses of Atracurium and Cisatracurium was administered atracurium had better neuromuscular blocking effect, spontaneous recovery and less residual paralysis postoperatively. Atracurium was preferred agent of choice for shorter duration procedures. Atracurium is a more effective neuromuscular blocking drug than cisatracurium at the same dose (2×ED95). On the other hand, higher dosages of cisatracurium, 0.2 mg/kg (4×ED95) and 0.3 mg/kg (6×ED95), result in longer duration of action, effective neuromuscular blocking, stable hemodynamic condition and no
clinically significant histamine release during surgery [5,6]

Cisatracurium has become one of the most widely used non-depolarizing neuromuscular blocking agent in patient population. It's rapid onset, longer duration of action, unique organ independent elimination and reduced side effects have made Cisatracurium an appealing alternative to older agents such as pancuronium and vecuronium.

Pediatric patients present unique challenges in anesthesia due to their physiological differences from adults, including variations in drug metabolism and sensitivity to anaesthetic agents [7].

Aim of the study was to compare the neuromuscular blocking effects of Atracurium and Cisatracurium in paediatric patients undergoing elective surgery under general anesthesia using neuromuscular monitoring [TOF].

Methodology:
A prospective, randomized controlled trial was designed to evaluate the efficacy and safety of two neuromuscular blockers in pediatric patients undergoing elective surgery under general anesthesia. The study was conducted at the Department of Anesthesiology, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pimpri, Pune, Dr. D. Y. Patil Vidyapeeth, Pune. The study was carried out from September 2022 to February 2024, with data collection spanning 18 months and analysis extending over 6 months. The study included patients aged 1 to 12 years, classified as ASA I or ASA II, scheduled for elective surgeries under general anesthesia and hemodynamically stable. Patients with known allergies to study drugs, difficult intubation, neurological, neuromuscular, cardiovascular disorders, impaired hepatic or renal function, and acute respiratory illness were excluded from the study.
A total of 60 patients were enrolled, divided equally into two groups of 30 patients each:
Group A: Inj. Atracurium (0.5 mg/kg) intravenously
Group B: Inj. Cisatracurium (0.15 mg/kg) intravenously.

Sample Size Calculation: Sample size was determined using the "WINPEPS" software (version 11.3), with a confidence interval of 95% and a power of 95%. Based on the anticipated mean onset times for Atracurium and Cisatracurium, the calculated sample size was 40 (20 per group). To enhance the validity of the results, the sample size was adjusted to 60 (30 per group).

Ethical Considerations: The study was approved by the Institutional Ethics Committee. Informed written consent was obtained from all participants' parents, who were briefed about the study's risks, benefits, and voluntary nature. Confidentiality of patient data was maintained throughout the study.

Preoperative Procedure: Patients underwent a pre-anesthetic evaluation and counseling the day before surgery, with a final review on the surgery day. Preoperative fasting guidelines were followed. Informed consent was obtained from the parents, detailing the benefits and side effects of the study drug. All patients had an intravenous cannula placed preoperatively.

Midazolam (0.02 mg/kg IV) was given to prevent separation anxiety of the child from the parents and INJ.GLYCOPYROLATE (0.004mg/kg) as premedication for anti-sialagogue effects.

On arrival to the operating room

1. All the standard monitors such as ECG, non-invasive blood pressure, SpO2, end tidal-carbon dioxide (EtCO2) were connected and baseline parameters noted.
2. The TOF monitor was attached which was used for neuromuscular monitoring

Induction:

Preoxygenation with 100% O_2. Induction was achieved with Fentanyl (1-2 µg/kg IV) and Propofol (1-2 mg/kg IV), monitored by loss of eyelash reflex or verbal response in older children. A mixture of 50% N_2O in O_2 and sevoflurane was used, with assisted ventilation via a Jackson Rees circuit. Muscle relaxants were administered according to the doses mentioned for each group within 5-10 seconds intravenously.

Group A received an intubating dose of Inj. Atracurium (0.5mg/kg)

Group B received an intubating dose of Inj. Cisatracurium (0.15mg/kg)

Neuromuscular monitoring was performed using TOF stimuli, with measurements taken every 15 seconds. Endotracheal intubation was performed once TOF O_2 and 50% N_2O, sevoflurane (1.8-2 MAC), and maintenance doses of muscle relaxants- A**tracurium:** 0.1 mg/kg and **Cisatracurium:** 0.03 mg/kg were given as and when required. Intraoperative hemodynamic parameters

Table 1: Cooper et al scoring system.

Score	Jaw relaxation	Vocal cord	Response to intubation
0	Poor	Closed	Severe coughing/bucking
1	Nominal	Closed	Mild cough
2	Moderate	Moving	Slight diaphragmatic movement
3	Good	Open	None

An intubation score of 8-9 was considered excellent, 6-7 good, 3-5 poor and 0-2 bad. Good to excellent intubation score were taken as clinically acceptable.

suppression was adequate, using the Cooper scoring system to assess intubation conditions and patient was connected to ventilator. Anaesthesia was maintained with were continuously monitored and maintained in normocapnia throughout the procedure.

Reversal of neuromuscular blockade was achieved with Neostigmine (0.005 mg/kg IV) and Glycopyrrolate (0.008 mg/kg IV) when TOF > 0.7. Patients were extubated with TOF > 0.9. Postoperatively, patients were monitored in the recovery room.

Statistical Analysis: Data were entered into a Microsoft Excel spreadsheet and analyzed using SPSS version 16. Descriptive statistics were used, and categorical variables were analyzed by using Chi-square test and Fisher's exact test. Repeated measures ANOVA was conducted to assess variations within and between groups over time. Statistical significance was set at $p < 0.05$.

Results:

A total of 60 patients were recruited during the study period and divided into two groups of 30 each.

Table 1 depicts comparison of demographic profile between two groups. The mean age in the

Group A (5.6±2.9 years) was higher compared to Group B (5.5±2.9 years). The mean weight Group B (18.5 ± 9.3) was higher compared to Group A (16.7 5 ± 8.02). Most of the patients in both the groups (Group A-70% and Group B- 40%) were male. The difference in both the study groups in terms of age, weight and gender distribution was not statistically significant when Chi square test was applied indicate that they were comparable (p>0.05).

Table 1: Comparison of demographic profile between two groups

DEMOGRAPHIC PROFILE	Group A (n=30)	Group B (n=30)	P value
Mean age	5.6 ± 2.9	5.5 ± 2.9	5.5 ± 2.9
Mean weight	16.7 ± 8.02	18.5 ± 9.3	0.43
Female Male	9 (30%) 21 (70%)	12 (40%) 18 (60%)	0.41

Data presented as n (%) and p-values using a chi-square test.

Table 2 compares the neuromuscular blocking effect in two groups.

Group A had a longer mean onset time (4.3 ± 0.46 minutes) compared to Group B (2.6 ±0.49 minutes). The difference in onset time between the two groups was statistically significant ($p < 0.001$).

Table 2: Distribution of onset time of neuromuscular block (NM) in two groups.

ONSET TIME OF NM BLOCKING EFFECT	Group A (n=30)	Group B (n=30)	p-value

Mean ± SD	4.3±0.46	2.6±0.49	**<0.001**

Data presented as n (%) and p-values using a chi-square test.

Table 3 depicts Group A had a shorter mean duration of NM block (27.8 ± 1.3 minutes) compared to Group B (54.9 ± 3.2 minutes) and the difference in the duration of NM block between the two groups was statistically significant ($p < 0.001$)

Table 3: Distribution of duration of neuromuscular block in two groups.

DURATION OF NM BLOCK	**Group A (n=30)**	**Group B (n=30)**	**p-value**
Mean ± SD	27.8±1.3	54.9±3.2	**<0.001**

Data presented as n (%) and p-values using a chi-square test.

Table 4 depicts Group A had a shorter mean time of recovery (27.4 ± 1.5 minutes) compared to Group B (37.8 ± 1.1 minutes) and the difference in the time of recovery between the two groups was statistically significant ($p < 0.001$).

Table 4: Distribution of time of recovery of neuromuscular blocking effect from the last dose of neuromuscular blockade in the two study groups.

TIME OF RECOVERY	**Group A (n=30)**	**Group B (n=30)**	**p-value**
Mean ± SD	27.4±1.5	37.8±1.1	**<0.001**

Table 5 depicts the distribution of jaw relaxation levels among the patients. In Group A, 18 patients (60%) exhibited good jaw relaxation, followed by moderate relaxation in 9 patients (30%). In Group B, 24 patients (80%) exhibited good jaw relaxation, whereas none of them experienced nominal jaw relaxation. The statistical analysis yielded a p-value of 0.108, indicating that the difference in jaw relaxation between the two groups was not statistically significant .

Table 5: Distribution of jaw relaxation in two groups.

Jaw relaxation	**Group A (n=30)**	**Group B (n=30)**	**P value**
Nominal	3 (10%)	0	0.108
Moderate	9 (30%)	6 (20%)	
Good	18 (60%)	24 (80%)	

Data presented as n (%) and p-values using a chi-square test.

Table 6 depicts vocal cord distribution in two groups. Hundred percent of patients in Group B had open vocal cords as compared to 86.7% of patients in Group A and the difference in the groups for vocal cords was statistically significant ($p = 0.04$)

Table 6: Distribution of vocal cord movements in two groups.

Cooper scoring	**Group A (n=30)**	**Group B (n=30)**	**P value**
Moving	4 (13.3%)	0	0.04
Open	26 (86.7%)	30 (100%)	

Data presented as n (%) and p-values using a chi-square test.

In table 7, Group A had 13 (43.3%) patients who had slight movement of diaphragm during intubation when compared to Group B where only 3 (10%) patients had slight movement of diaphragm. The difference in the groups was statistically significant (p=0.004)

Table 7 : Distribution of intubating condition in two groups.

Cooper scoring	Group A (n=30)	Group B (n=30)	P value
Slight movement of diaphragm	13 (43.3%)	3 (10%)	0.004
None	17 (56.7%)	27 (90%)	

Data presented as n (%) and p-values using a chi-square test.

In table 8 comparing the grades of Cooper scoring between two groups, Group B 27 (90%) patients had an excellent intubating condition whereas 20 (66.7%) patients in Group A had excellent. Hence Group B provided better intubating conditions when compared to Group A and the difference in the groups was statistically significant (p = 0.03) (Table 6).

Table 8: Distribution of grades of Cooper scoring in two groups.

Grades of Cooper scoring	Group A (n=30)	Group B (n=30)	p-value
Good (score of 6-7)	10 (33.3%)	3 (10%)	0.03
Excellent (score of 8-9)	20 (66.7%)	27 (90%)	

Data presented as n (%) and p-values using a chi-square test.

Table 9 depicts that both groups had similar baseline heart rates and heart rates after injecting the drug. During laryngoscopy, at 1-minute post-intubation, and at 15 minutes post-intubation, Group A had higher mean heart rates compared to Group B and there were statistically significant differences (p < 0.001) between the two groups

Table 9: Heart rate distribution in two groups at different intervals

Heart Rate (Mean± SD)	Group A (n=30)	Group B (n=30)	P value
Baseline	109.7±7.3	109±9.6	0.75
After injecting drug	111.8±6.3	111.9±7.5	0.98
During laryngoscopy	114.6±6.9	105.4±8.1	**<0.001**
Post intubation 1 min	116.4±4.6	107.8±8.2	**<0.001**
Post intubation 5 min	111.9±6.06	109.1±7.5	0.11
Post intubation 10 min	113.1±5.08	110.9±6.3	0.14
Post intubation 15 min	114.8±4.8	111.1±4.9	0.004

Post intubation 30 min	115.2±4.7	114.6±4.7	0.58
During extubation	118.6±5.3	119.2±4.01	0.62
10 min after extubation	114.8±4.1	116±5.03	0.31

Table 10 depicts the baseline Mean arterial pressure values (MAP) were similar between the two groups and after injecting the drug, there was a slight decrease in MAP in both groups. During laryngoscopy and the immediate post-intubation period (1 min, 5 min), there was a transient increase in MAP in both groups and from 10 minutes post-intubation onwards, the MAP gradually decreased in both groups. During extubation and 10 minutes after extubation, the MAP remained comparable between the two groups and there were no statistically significant differences observed between Group A and Group B ($p > 0.05$)

Table 10: Mean arterial blood pressure distribution in two groups at different intervals

MeanArterial Pressure (Mean ± SD)	**Group A (n=30)**	**Group B (n=30)**	**p-value**
Baseline	86.1±9.3	89±8.9	0.22
After injecting drug	84±9.4	84.9±8.2	0.69
During laryngoscopy	90.03±9.3	90.4±8.4	0.86
Post intubation 1 min	92.7±9.3	94.4±7.9	0.44
Post intubation 5 min	86.1±9.2	86.8±9.07	0.77
Post intubation 10 min	84.1±9.2	85.2±9.7	0.64
Post intubation 15 min	82.1±9.2	83.9±9.08	0.45
Post intubation 30 min	79.8±9.2	80.07±8.2	0.93
During extubation	90.1±9.2	92.6±9.3	0.29
10 min after extubation	81.8±9.2	83.07±8.9	0.61

Table 11 compares the side effects between the two groups. Erythema was seen in 3.3% of patients in Group A and 10% of the patients in group A had flush when compared to Group B 3.3%. There was no statistically significant difference in the two groups ($p=0.11$)

Table 11: Distribution of side effects in two groups.

Side effects	**Group A (n=30)**	**Group B (n=30)**	**p-value**
Erythema	1 (3.3%)	0	0.11
Flush	3 (10%)	1 (3.3%)	
Absent	26 (86.7%)	29 (96.7%)	

Data presented as n (%) and p-values using a chi-square test.

DISCUSSION

In our study, the mean age in Group A (5.6±2.9 years) was higher compared to Group B (5.5±2.9 years), but this difference was not statistically significant, indicating that the groups were comparable. The mean weight was higher in Group B (18.5±9.3 kg) compared to Group A (16.7±8.02 kg), but this difference was also not statistically significant ($p>0.05$). Most patients in Group A (70%) and Group B (60%) were male, with no significant difference in gender distribution ($p>0.05$). Therefore, participants in both groups had comparable characteristics regarding age, weight, and gender distribution.

Group A had a longer mean onset time (4.3 ± 0.46 minutes) compared to Group B (2.6 ± 0.49 minutes), a statistically significant difference ($p < 0.001$). Shruthi et al [8] reported similar findings with cisatracurium showing a faster onset time of 2.7±0.12 minutes compared to atracurium's 3.28±0.64 minutes.

The mean duration of neuromuscular block (NM block) was shorter in Group A (27.8 ± 1.3 minutes) compared to Group B (54.9 ± 3.2 minutes), a statistically significant difference ($p < 0.001$). Ranjan P et al [9] found that the cisatracurium group had a significantly longer duration of action (70.14 ±1.87 minutes) compared to the atracurium group (44.9 ±2.45 minutes). Bluestein et al [10] found that increasing the cisatracurium dose from 0.1 to 0.15 and 0.2 mg/kg decreased the mean onset time from 4.6 to 3.4 and 2.8 minutes, respectively, and increased the mean clinically effective duration from 45 to 55 and 61 minutes. C.E. Smith [11] found no significant difference in the duration of action between atracurium and cisatracurium ($p >0.05$).

The mean recovery time was shorter in Group A (27.4 ± 1.5 minutes) compared to Group B (37.8 ± 1.1 minutes), a statistically significant difference ($p < 0.001$). M. T. Carroll [12] found that cisatracurium 0.15 mg/kg took longer (51–59 minutes) for 25% recovery compared to cisatracurium 0.1 mg/kg (45–48 minutes) and atracurium 0.5 mg/kg (47–48 minutes), but the differences were not statistically significant.

In terms of intubating conditions, 90% of patients in Group B had excellent conditions compared to 66.7% in Group A, a statistically significant difference ($p = 0.03$). This aligns with Athaluri VV et al [13]. found that 42% and 40% of patients had excellent and good intubating conditions with cisatracurium 0.1 mg/kg, and 72% and 24% with cisatracurium 0.15 mg/kg, while 38% and 42% had these conditions with atracurium 0.5 mg/kg. The differences were statistically significant.

Regarding hemodynamic profiles, Group A had higher mean heart rates during laryngoscopy and post-intubation compared to Group B, with significant differences ($p <0.05$). Systolic and diastolic blood pressure (SBP and DBP), mean arterial pressure (MAP), and oxygen saturation (SpO2) were comparable between the groups at various intervals, with no statistically significant differences. El-Kasaby et al.[6] found significant HR and MABP increases with 2×ED (95) doses of atracurium and cisatracurium, but not with higher cisatracurium doses. Arun Kumar Mohanty et al [14]. and Harpreet Kaur et al [15] found no significant hemodynamic differences between atracurium and cisatracurium ($p >0.05$). Our study's findings were consistent with these results.

Side effects were minimal, with erythema seen in 3.3% of patients in Group A and 10% having flush compared to 3.3% in Group B. This difference was not statistically significant ($p>0.05$). Ranjan R et al.[16] reported 2% erythema and 2% flush with atracurium (0.5 mg/kg), while cisatracurium (0.15 mg/kg) had no adverse effects. These findings align with our study.

Our study showed, Group B had faster onset, longer duration, and better intubating conditions with comparable hemodynamic profiles and minimal side effects compared to Group A, aligning with findings from other studies.

Strengths and Limitations:

One of the strengths of our study is the use of standardized neuromuscular monitoring techniques (TOF stimulation) ensures accurate and reliable measurements of neuromuscular function.

However, there are several limitations to consider. Our sample size though calculated to be sufficient for detecting differences in primary outcomes, may not be large enough to detect rare adverse effects. Our study population was limited to pediatric patients undergoing elective surgery, which may limit the generalizability of our findings to other patient populations or emergency surgical settings. Finally, while we monitored hemodynamic parameters and adverse effects, cost-effectiveness were not assessed.

Implications to Practice:

The findings from our study have several implications. For pediatric patients undergoing short duration surgeries, Atracurium's short duration of action and rapid recovery profile may be advantageous. However, for longer duration procedures or in patients where hemodynamic stability is a concern, Cisatracurium appears to be the preferable choice due to its longer half life and minimal cardiovascular side effects.

CONCLUSION

The results of our study provide valuable insights into comparing the neuromuscular blocking effects of atracurium and cisatracurium in paediatric patients undergoing elective surgery under general anaesthesia using neuromuscular monitoring. The findings demonstrated significant differences between atracurium and cisatracurium in terms of onset time, duration of action,

recovery profile and intubating conditions. Overall, cisatracurium exhibited a more rapid onset of action, longer duration of neuromuscular blocking effect and superior intubating conditions compared to atracurium. However, atracurium was associated with a shorter recovery time of

neuromuscular blocking effect after the last dose of neuromuscular blockade. The choice between the two neuromuscular blocking agents should be based on quick onset of action, good intubating condition, longer duration, superior hemodynamic stability, good spontaneous reversibility and less or no side effects

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