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ORIGINAL RESEARCH

Comparative Study of the Use of Cisatracurium and Atracurium in Children under General Anaesthesia

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Abstract

Background: Cisatracurium and atracurium are intermediate-acting muscle relaxants without many side effects due to non-organ-dependentnon-organ-dependent Hoffmann elimination. Cisatracurium in clinical practice is more potent and devoid of histamine-related side effects than atracurium but its use in children is limited.
Objective: To compare cisatracurium and atracurium in children regarding the onset, intubating conditions, duration of action, and reversibility of neuromuscular blockades.
Methods: This study was a prospective, randomised, double-blinded study on 83 children aged 2-7 years belonging to ASA I and II who were allocated into two groups of 42 patients in Group I and 41 in Group II. Group I received Cisatracurium 0.15mg/kg as the loading dose and 0.03mg/kg as the maintenance dose. In comparison, Group II received Atracurium 0.5mg/kg as the loading dose and 0.1mg/kg as the maintenance dose. The maintenance dose of neuromuscular blocking agent was given after 25% recovery of initial TOF value. The onset time, duration of block and recovery index were recorded using a train of four responses and a haemodynamic profile.
Results: The difference in mean onset time was significant among the two groups (2.47±0.59 minutes vs. 2.12±0.62minutes in the cisatracurium and atracurium groups, respectively). The mean duration of action of cisatracurium was also significantly longer (47.03±9.15 minutes) compared to that of the atracurium group (27.90±9.73 minutes). Both groups had excellent intubating conditions; haemodynamics and reversibility time were also comparable.
Conclusion: Cisatracurium is also a potent neuromuscular blocker in comparison to atracurium, which can be used safely in children undergoing surgeries of more than 45 minutes duration.

Keywords: Atracurium, Cisatracurium, Neuromuscular monitoring, Non-depolarising neuromuscular blockers, Paediatric Anaesthesia.

Introduction

Tracheal intubation is required during general anaesthesia for ventilation and oxygenation as well as for anaesthetic gas delivery. Several classes of medications are used to achieve successful intubation with minimum complications, like hypnotics, analgesics and neuromuscular blocking agents. [1] Neuromuscular blocking agents play an

essential role in general anaesthesia. These are primarily used to facilitate endotracheal intubation and to achieve better surgical conditions. These are used to prevent sudden movements and obtund reflexes, thereby allowing controlled ventilation during surgery. Rapid onset, adequate muscle relaxation, haemodynamic stability, and complete return of skeletal muscle function are the main requirements that neuromuscular blocking agents should fulfil. Intermediate-acting non-depolarising muscle relaxants like vecuronium, atracurium and rocuronium are commonly used to achieve these goals. Cisatracurium is another relatively newer, non-depolarising, intermediate-acting neuromuscular blocking agent, a stereoisomer of atracurium. It is found to be approximately three times more potent than atracurium, and its maximum duration of action is longer than an equipotent dose of atracurium. Its metabolism is little affected by liver or kidney diseases. Hence, it produces clinical benefits similar to atracurium while minimising side effects related to histamine release and laudanosine accumulation. [2,3] Despite these benefits, cisatracurium has limited use in children as it has been reported to have a slower onset and less satisfactory intubating conditions than other neuromuscular blocking agents when used in equipotent doses. [4,5] To understand this discrepancy, the present study was conducted in order to compare the onset, duration of action and intubating conditions after equipotent doses of cisatracurium and atracurium in children.

Methods

This prospective, randomised, double-blinded study was conducted in a tertiary care centre after ethical approval was obtained from the institute ethics committee (certificate number: IEC/Th/18/Anst19). Eighty-three children (aged 2–7 years old) of either sex, belonging to American Society of Anaesthesiologists (ASA) physical status classification I and II, scheduled for any elective surgery of more than forty-five minutes duration under general anaesthesia, were included in the study.

Children with anticipated difficult intubation, a history of drug intake known to interact with NMBAs, a history of seizures, hypersensitivity to the study drugs, congenital heart disease, and metabolic and neuromuscular disorders were excluded from the study. The children were assessed preoperatively, and investigations were done as per the surgery requirement. The purpose and protocol of the study were explained and informed written consent was obtained from all the children's parents/guardians. The children were fasted prior to surgery as per institutional fasting guidelines. Standard monitors like electrocardiography (ECG), non-invasive blood pressure (NIBP), capnograph and pulse oximeter were attached upon arrival at the operation theatre. The baseline vital signs were recorded. Before the induction of general anaesthesia, surface electrodes were placed over the ulnar nerve at the wrist for neuromuscular monitoring using the TOF monitor (TOF watch SX acceleromyography device, Ireland).

The children were randomly assigned using computer-generated random numbers to either of two groups: Group I (n = 42) who received an initial bolus dose of 0.15mg/kg of cisatracurium and maintenance dose of 0.03mg/kg or Group II (n = 41) who received an initial bolus dose of 0.5mg/kg of atracurium and maintenance dose of 0.1 mg/kg. The maintenance doses of neuromuscular blocking agent were given after 25% recovery of initial TOF value.

The drugs were prepared accordingly and labelled by an anaesthesiologist who was not participating in the further recording of data and patient management. The children in both groups were given general anaesthesia using a standard protocol as per the acceptability of the patient. Pre-oxygenation with 100% Oxygen was started using the Jackson and Rees circuit for three minutes. Induction of anaesthesia was done either by sevoflurane or intravenous anaesthesia using propofol 2mg/kg (after establishing intravenous access and administering glycopyrrolate 5μgkg^{-1} and fentanyl 2μgkg^{-1} as premedication), targeting to achieve MAC value of 1. After checking the

adequacy of mask ventilation, a loading dose of the neuromuscular blocking agent (NMBA), as per the Group allocated, was administered intravenously, and this timing was noted (T_0). Neuromuscular monitoring was done using a Train of Four (TOF) monitor (TOF watch SX acceleromyography device, organon) for which transcutaneous stimulation of the ulnar nerve was done with supramaximal stimuli of 0.2ms duration at 2 Hz every 15 seconds and mechanical twitch response of adductor pollicis muscle and TOF values were observed. Neuromuscular monitoring was assessed according to the number of twitches: four twitches showed 0-75% of the receptors were blocked, three twitches showed at least 75% of the receptors were blocked, two twitches showed 80% of the receptors were blocked, and only one twitch showed that 90% of the receptors were blocked.[6,7] On achieving a TOF score of 0, the children were intubated by a senior resident doctor or consultant with at least three years of experience using an appropriate-sized endotracheal tube. This time was noted (T_1). Intubating conditions were assessed as "excellent" with easy passage of tube without coughing, vocal cords relaxed with no movement and abducted, "good" with slight coughing and/or bucking with passage of tube, and the vocal cords were relaxed and abducted, "poor" with moderate coughing and/or bucking with passage of tube, vocal cords relaxed and moderately adducted or "inadequate" with vocal cord not relaxed, and tightly adducted.[5] Haemodynamic parameters including the heart rate (HR), systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), and oxygen saturation (SpO_2) and $EtCO_2$ (end-tidal CO_2) were measured at baseline before induction, just after giving induction agent, then at 1, 3 and 5 minutes after intubation and after extubation.

Anaesthesia was maintained by the standard anaesthesia technique, using O_2 in 67% N_2O and sevoflurane to achieve MAC = 1. The neuromuscular blocking agent was repeated in $1/5^{th}$ of the loading dose after 25% recovery of TOF. The time of giving the first repeat dose was noted (T_2). Duration of action (DOA) was taken as the time from giving a loading dose of NMBA until 25% recovery of TOF, which was reported (T_0-T_2). The rest of the procedure was allowed to proceed as routine. At the end of surgery, all anaesthetic agents were withdrawn. Neuromuscular blockade was reversed using inj. Glycopyrrolate 10µg/kg and inj. Neostigmine 0.05mg/kg after 25% recovery of TOF was achieved. The duration from administration of the reversal agent till the appearance of reflexes and adequate muscle power (on attainment of 80% recovery from neuromuscular blockade) was noted as the duration of reversibility from neuromuscular blockade (Tr) and the children were extubated. The haemodynamic parameters of the children were pointed out at this time, and the children were transferred to the recovery room and, thereafter, to the ward. The side effects of drugs in the form of local reactions such as erythema, flushing and wheals, as well as complications, if any, like bradycardia, hypotension, rash, and bronchospasm, were noted.

Data management

The researchers recorded the mean duration of action as 37.6±10.2 minutes in the Cisatracurium group (Imbeault *et al.*) as against 31.5±6.01 minutes in the Atracurium group (Ribeiro *et al.*). [8,9] Assuming these are reference values, the minimum required sample size is at a 5% significance level, and 95% power is needed for at least 40 patients in each Group. Data was collected from these children according to the methodology of the study. Quantitative variables were presented as mean (± SD), while qualitative variables were expressed as frequencies and percentages. An unpaired t-test was used to compare quantitative variables between study groups. Qualitative or categorical variables between groups were compared using the Chi-Squared test. Statistical analysis was performed with the SPSS statistical package (version SPSS 16.0). A p-value less than 0.05 was considered statistically significant.

Result

A total of 83 children were enrolled in the study, of which three patients were excluded due to non-fulfilment of inclusion criteria, while 80 children were eventually included (Figure 1).

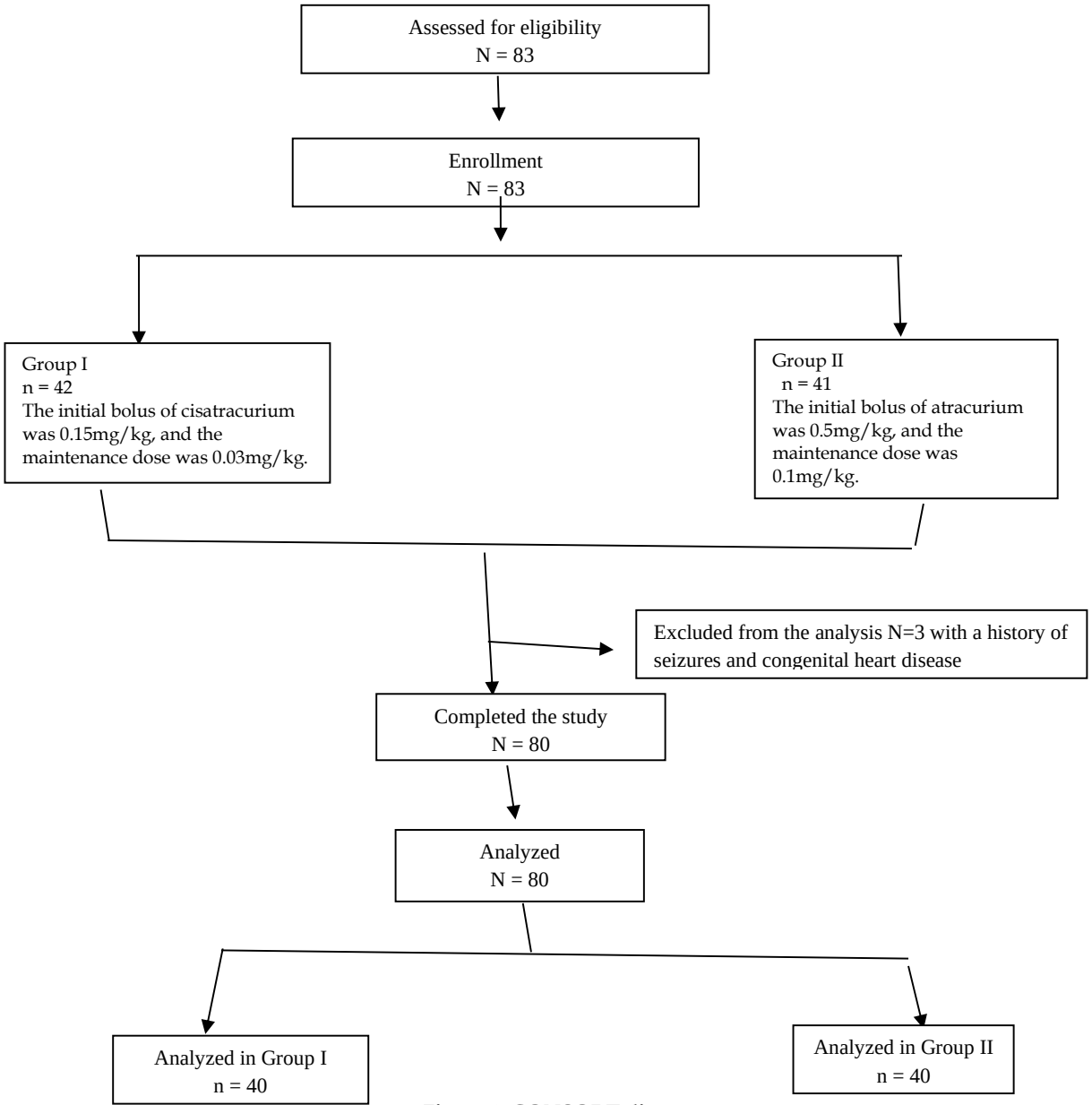

Figure 1: CONSORT diagram

Table I: Demographic profile of the study subjects

Variable	*Group I*	*Group II*	*p-value*
Mean Age (Years)	4.55 ± 2.02	4.35 ± 2.01	0.658
Sex (F/M)	12/28	13/27	0.809
ASA grade (I/II)	38/2	40/0	0.494

The demographic profile was comparable in both groups (Table I). Intubating conditions are shown in Table II. In Group I, 95.0% of the patients had excellent intubating conditions, while 5.0% had good intubating conditions. In Group II, 100% of the patients had excellent intubating conditions. When the groups were compared, the difference in intubating conditions lacked statistical significance (Table II and Figure 2).

Table II: Grading of intubating conditions in the two arms of the study

Intubating conditions	*Group I Frequency*	*Percentage*	*Group II Frequency*	*Percentage*	*p-value*
Excellent	38	95.0	40	100.0	0.494
Good	2	5.0	0	0.0	
Total	40	100	40	100	

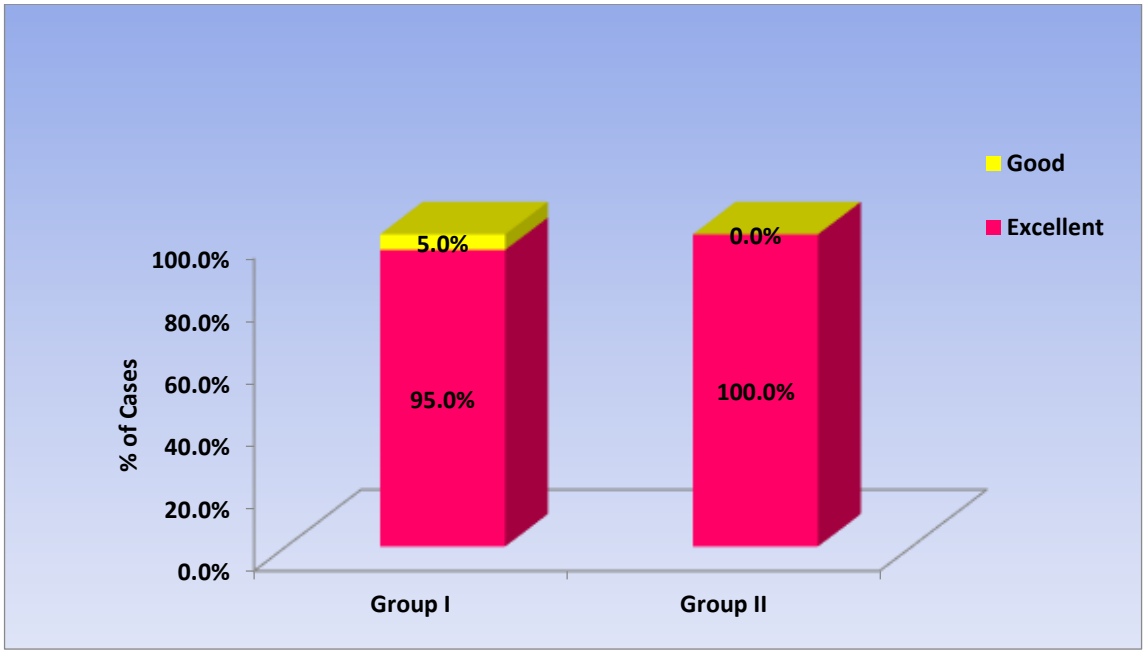

Figure 2: Grading of Intubating conditions in the two study groups

Table III presents the time of onset, duration of action, and time of reversibility. The onset time was recorded as the time to reach TOF = 0. The time of onset of cisatracurium (Group I) was 2.47±0.59 minutes, which was significantly longer than 2.12±0.62 minutes for atracurium (Group II) (p = 0.014).

Table III: Time Intervals showing onset, intervals and reversibility of study drugs

	Group I Mean ± SD	*Group II Mean ± SD*	*p-value*
Onset (T1-T0)	2.47 ± 0.59	2.12 ± 0.62	0.014
Duration of action of first dose (T2-T0)	47.03 ± 9.15	27.90 ± 9.73	<0.001
Reversibility (Tr)	2.10 ± 0.83	1.90 ± 0.52	0.447

The duration of action of cisatracurium was observed to be longer than that of atracurium in children. The mean duration of action of the first dose of cisatracurium in Group I was 47.03±9.15 minutes compared to 27.90±9.73 minutes in Group II ($p < 0.001$). The time of reversibility (recovery of TOF from 25% to 80% after giving reversal agent) in Group I was 2.10±0.83 minutes compared to 1.90±0.52 minutes in Group II (Table III, Figure 3). The heart rate and mean BP variations during the intra-operative period were comparable in both groups (Figures 4 and 5).

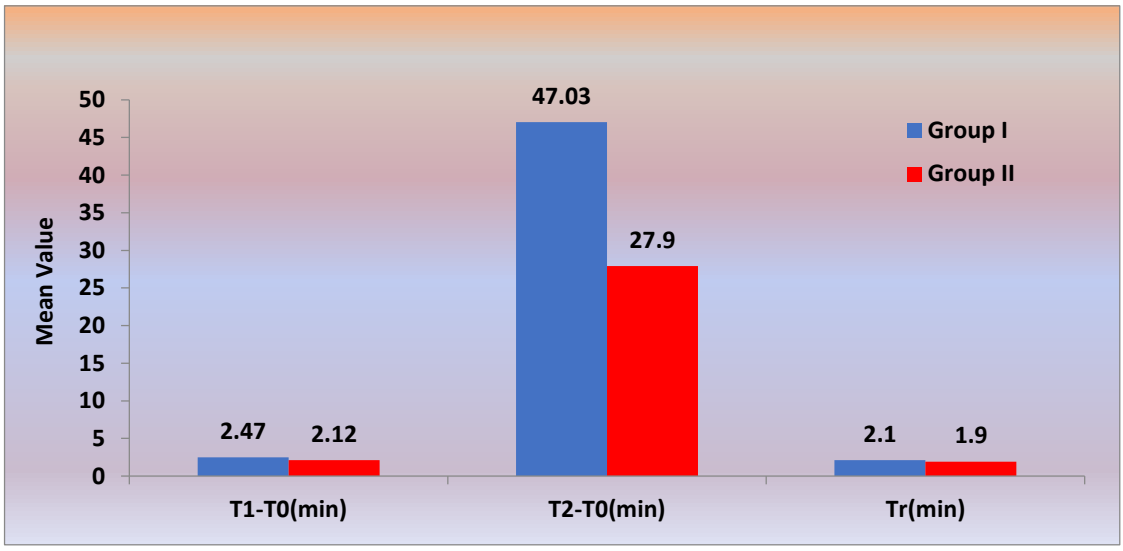

Figure 3: Comparison of time intervals showing onset, time intervals and reversibility

Discussion

A neuromuscular blocking agent plays a pivotal role during general anaesthesia. It should produce rapid and adequate muscle relaxation with predictable and complete recovery of skeletal muscle function after surgery. It should be haemodynamically stable with minimum side effects. Various neuromuscular blockers have been used to achieve these goals. Cisatracurium is a newer non-depolarising intermediate-acting benzylisoquinoline neuromuscular blocking agent which has a 1 R-cis, 1 prime R- cis configuration, and it is one of the ten stereoisomerisms of atracurium. It was isolated due to its ability to produce a similar neuromuscular block to atracurium without the adverse side effects due to histamine release at high doses and laudanosine accumulation in the plasma. Its decomposition occurs in the blood plasma and extracellular fluid at standard temperature and pH (Hoffmann degradation); hence, liver or kidney diseases do not affect muscle relaxation recovery. [2,3] Various studies have been conducted earlier to determine the pharmacokinetics, pharmacodynamics, safety and efficacy of cisatracurium and atracurium in adults, but few comparative studies have been done in children. [4,5]

In this study, eighty paediatric patients from the 2-7 years age group scheduled for surgery under general anaesthesia were randomly allocated into two groups of 40 patients each. Group I received 0.15 mg kg-1 cisatracurium, and Group II received 0.5 mg kg-1 atracurium. The dose chosen for atracurium was 0.5 mgkg-1, the usual dose recommended for children. Different doses of cisatracurium have been studied, and the 3× ED95 dose, i.e. 0.15 mgkg-1, was found to be optimal, as described by Shang Guan *et al.* and many others in their studies.[10] Hence, these doses were compared in the present study.

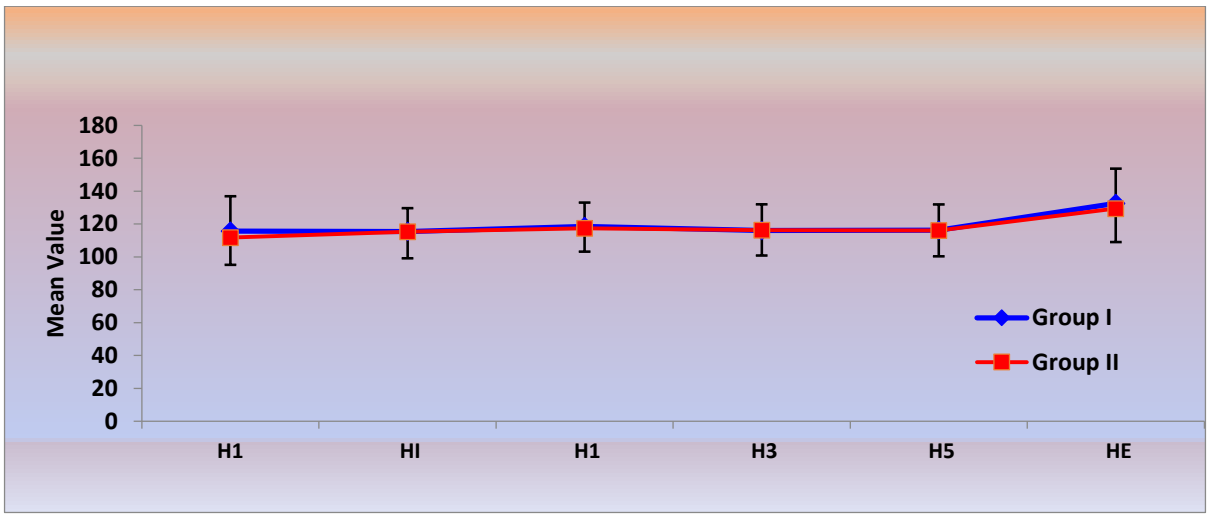

Figure 4: Comparison of heart rate between two groups

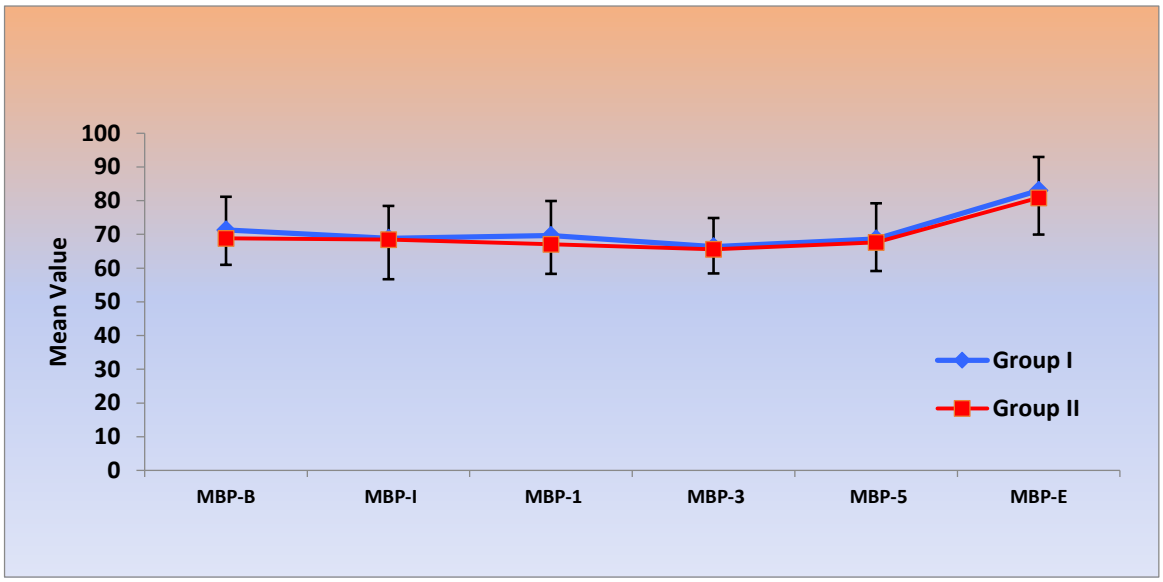

Figure 5: Comparison of mean BP between two groups

In this study, both groups were comparable in their demographic profile. The baseline investigations, as well as baseline heart rate and blood pressure, were also similar in the two groups. The doses of cisatracurium and atracurium used in the study induced the same trend of heart rate in both groups till the study was completed. HR did not vary much after giving the induction agent. Tachycardia was observed after intubation and extubation in both study groups. This was possibly due to the stress response of laryngoscopy, intubation and extubation. However, this increase in heart rate was not statistically significant. No patient developed a decrease or increase in heart rate >20% of baseline attributable to neuromuscular blocker administration. Mean Arterial Pressure (MAP) value decreased in both groups after giving an induction agent but remained consistent after intubation; however, after

extubation, MAP increased in both study groups. When compared between the groups, the difference in MAP lacked statistical significance. These observations agree with the study conducted by Karadeniz *et al.*, in which no significant difference in HR and MAP was observed at any point in the cisatracurium and atracurium study groups. [11] Taivainen *et al.* also found the haemodynamics comparable while studying different doses of cisatracurium in children.[12]

In Group I, 95% of patients had excellent intubating conditions, while 5% had good intubating conditions. In Group II, all the patients had excellent intubating conditions. Almost every patient in both groups had satisfactory intubating conditions. Hence, they were comparable in both groups (p = 0.494), a finding by the study done by Karadeniz *et al.* and Voss *et al.*, who also found similar intubating conditions using equipotent doses of atracurium and cisatracurium. [11,13]

In the present study, the neuromuscular blockade effect of the study drugs was assessed using a TOF monitor by detailing the response of adductor pollicis to the supramaximal train of four stimulation of the ulnar nerve at 2.0 Hz every 15 seconds to compare the time of onset (T_1-T_0), clinical duration of action (T_2-T_1) and time of reversibility (Tr) in children, which is by the standard practice. In this study, the mean time of onset of neuromuscular blockade was found to be 2.47±0.59 minutes with 0.15 $mgkg^{-1}$ cisatracurium, while it was 2.12±0.62 minutes with 0.5 $mgkg^{-1}$ atracurium. This difference in the mean time of onset was significant. This is in accordance with the results of Voss *et al.*, who also found shorter onset times when atracurium was given to children.[13] However, when compared with cisatracurium, the difference was statistically insignificant, probably because of a lower dose of cisatracurium (0.1 mg kg^{-1}) used in that study. The results of the present study are consistent with the studies conducted by Shang Guan W et al., wherein the onset time for 0.15 $mgkg^{-1}$ dose of cisatracurium was observed to be 2.3±0.2 minutes.[10] Imbeault *et al.* [8] conducted a similar study but with different doses of cisatracurium. They recorded a time of onset of 2.5±0.8 minutes with 0.1 $mgkg^{-1}$ dose of cisatracurium in children aged 1-6 years, similar to that observed in the present study. George, in his review of NMBAs in children, also found that after administering a dose of 0.15 $mgkg^{-1}$ cisatracurium, the onset of maximum block occurred in three minutes, while it occurred in 1.4 minutes after a standard dose of 0.5 $mgkg^{-1}$ atracurium.[14] This is in accordance with the present study. Taivainen *et al.* used 0.15 $mgkg^{-1}$ of cisatracurium in 27 infants and 24 children 2-12. They found a mean onset time of 2.0±0.8 minutes and 3.0±1.2 minutes, respectively, a possible variation with increasing age.[12]

The mean duration of action of the first dose of cisatracurium was significantly longer (47.03±9.15 minutes vs. 27.90±9.73 minutes) than that of atracurium in the present study. This difference could be because non-depolarising neuromuscular blockers of high potency, like cisatracurium, have fewer molecules to diffuse from the central compartment into the effect compartment. Buffered diffusion occurs in these drugs and causes repetitive binding and unbinding to receptors, which keep potent drugs in the neighbourhood of the effectors' sites and potentially lengthens the duration of effects.[15] The findings in the present study agree with the observation made by George, who, in his review, concluded that the duration of action of cisatracurium is longer than that of atracurium in children. [14] The results are contrary to Voss *et al.*, who found a comparable duration of action (34.1±5.5 minutes for atracurium and 34.1±6.5 minutes for cisatracurium. [13] This may be due to the lower dose used in that study. The duration of action of cisatracurium in the present study was comparable to that reported by Imbeault *et*

al., Shang Guan *et al.* and Taivainen *et al.* on giving a similar dose of 0.15 mg kg^{-1} of cisatracurium in children. [8,10,12]

The time of reversibility was measured as the duration of giving of injection neostigmine after 25% recovery from neuromuscular blockade till 80% recovery of TOF is achieved. Both groups demonstrated comparable mean time of reversibility. These results are similar to those of Voss *et al.*, who found comparable time of reversibility among both groups. However, the time of reversibility in both groups was much shorter in the present study due to the reversal of neuromuscular blockade by neostigmine, whereas Voss *et al.* allowed spontaneous recovery. [13] Imbeault *et al.* and Shang Guan *et al.* also found time of reversibility of 10.9±3.7 minutes and 9.1±2.3 minutes, respectively, without the use of a reversal agent, with 0.15mgkg^{-1}dose of cisatracurium in children. [8,10]

In the present study, no signs of histamine release like flushing, erythema, and itching were noted in any child receiving cisatracurium or atracurium. These observations are similar to those made by Taivainen et al., who also used identical doses.[12] Voss *et al*. observed urticaria in six out of 42 patients in the atracurium group, whereas no patient developed urticaria in the cisatracurium group. However, the two groups had no significant difference in the overall side effect profile.[13] George also concluded that the dose of cisatracurium up to 3 × ED_{95} in children and up to 6-8 × ED_{95} in adults produce no sign of histamine release or significant changes in heart rate and blood pressure.[14]

This study also has a few limitations. Only children aged 2-7 and children in the ASA physical status I and II were included. The study was also limited to one geographical area only. Therefore, future multicentre studies with different patient strata are recommended.

Conclusion

This study concludes that in comparison to atracurium, cisatracurium is also a potent neuromuscular blocking agent which can be used safely in paediatric patients. Although the onset time is longer, the duration of the blockade is prolonged, the haemodynamics are well maintained, and there are no signs of histamine release. With its use, intubation can be accomplished with suitable to excellent intubating conditions within three minutes following 0.15 mgkg^{-1} dose of cisatracurium. Therefore, it is recommended that cisatracurium is a good alternative to other neuromuscular blockers as it provides optimal conditions to facilitate endotracheal intubation, a longer duration of action with dose 3×ED_{95}, haemodynamic stability and smooth recovery, which may prove it to be a suitable choice for children undergoing routine general surgeries of more than 45 minutes duration.

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