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Comparison of three different doses of cis-atracurium under isoflurane anesthesia

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ABSTRACT

Aims: In this study; we compared the effects of three different doses of cis-atracurium, a nondepolarizing muscle relaxant agent, on neuromuscular blockade duration, endotracheal intubation quality and hemodynamic parameters under isoflurane anaesthesia.

Methods: A total of 60 patients (ASA I-II) were included in the study. Patients were premedicated with 10 mg diazepam intramuscularly 45 minutes before the operation. After the patients were transferred to the operating room, they were monitored noninvasively for heart rate and arterial blood pressure. Train of Four (TOF)-GUARD acceleration monitor was used for neuromuscular evaluation. All patients were administered 1 mg/kg fentanyl and 2 mg/kg propofol at induction, and anaesthesia maintenance was provided with 1.5% isoflurane+50% N_2O+50% O_2. The patients were divided into three groups according to the dose of cisatracurium administered: 0.15 mg/kg was administered to Group 1, 0.20 mg/kg was administered to Group 2, and 0.40 mg/kg cis-atracurium was administered to Group 3. Endotracheal intubation was performed at 120 seconds, and the block time of 99-100% (effect onset time) was recorded.

Result: Although the endotracheal intubation quality was evaluated as excellent and/or good in all three groups, the intubation quality of Group 3 was statistically higher than the other two groups ($p<0.05$). In hemodynamic measurements, no significant difference was observed within and between groups in all three groups. While the onset of effect was significantly shorter in the third group compared to the other two groups, the clinical effect duration was more prolonged. No significant difference was observed between all three groups regarding the postoperative recovery period and quality.

Conclusion: The 0.4 mg/kg application dose of cis-atracurium is superior to other recommended dose groups due to its high intubation quality, short onset of action, not causing any severe hemodynamic changes or side effects, and good recovery quality and duration.

Keywords: Cis-atracurium, neuromuscular block quality, general anaesthesia, nondepolarizing muscle relaxant

INTRODUCTION

The provision of anaesthesia is an essential component of healthcare worldwide. Access to safe anaesthesia is considered a fundamental individual right, and guidelines are published for its safe implementation.[1,2] Therefore, it is critical that the healthcare system can provide safe and effective anaesthesia for a wide range of surgical procedures in children and adults. However, many difficulties are encountered in providing anaesthesia, especially in the developing world, where facilities, equipment and staff training are often inadequate.[3] In general anaesthesia, patients are unconscious and do not realize their surroundings, but in practice, general anaesthesia is far beyond a state of unconsciousness. The components of general anaesthesia are analgesia, amnesia, muscle relaxation and limitation of autonomic reflexes.[4] There is no single drug used for general anaesthesia that provides all elements of general anaesthesia goals. Therefore, a combination of drugs, including volatile anaesthetics, opiates and at least muscle relaxants, is used during general anaesthesia.[4]

In anaesthesia, advances in neuromuscular muscle relaxants and the introduction of new drugs into clinical use have provided great flexibility for anesthesiologists.[5] None of the currently available muscle relaxants meets the criteria for an ideal neuromuscular blocking agent described by Savarese and Kitz.[6] Cis-atracurium Besylate (51W89 besylate, Nimbex) is the R-cis-R' isomer of Atracurium and is three times more potent. Although their muscle relaxant effects are similar, their onset of action initiates later.[7,8] Side effects observed with atracurium due to dose-dependent histamine discharge were not observed with cis-atracurium.[9]

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Although it has long been acknowledged that the onset of action of nondepolarizing muscle relaxants can be shortened by using large doses, use in these doses both increases the duration of clinical effects and increases the possibility of side effects.[10]

In our study, in isoflurane anaesthesia, using cis-atracurium at doses of 0.15 mg/kg, 0.20 mg/kg and 0.40 mg/kg, we evaluated intubation quality, maximum effect onset time, clinical effect duration, effects on hemodynamic parameters, effects on recovery and we aimed to compare side effects.

METHODS

Study Design

Our prospective thesis study, observational, single-centre study was initiated after obtaining the ethics committee's consent at the Anesthesiology and Reanimation Clinic of the Ministry of Health Ankara Training and Research Hospital. All procedures performed in our study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration (as revised in 2013) and its later amendments or comparable ethical standards.

Patients

Our study included 60 patients between the ages of 18-65, whose operating time did not exceed 2 hours, who did not have cardiovascular, pulmonary, renal, hepatic, neurological, psychiatric, neuromuscular, inflammatory or endocrine diseases and who did not use any medications that would affect the neuromuscular junction. Patients who were pregnant or suspected of pregnancy and who were taken as emergency cases were excluded from the study. Additionally, patients who required additional neuromuscular support other than induction during the operation were also excluded from the study.

Interventions and Clinical Definitions

All patients were premedicated with 10 mg diazepam intramuscularly 45 minutes (min) before the operation. Patients transferred to the operating theatre were monitored noninvasively for heart rate and blood pressure. For neuromuscular monitoring, the Train of Four (TOF)-GUARD INMT (Biometer, Denmark) acceleration monitor was placed on the arm ulnar nerve trace, the piezoelectric acceleration transducer on the thumb distal phalanx, and the skin temperature sensor on the adductor pollicis muscle, after the skin was cleansed with alcohol. Before induction of anaesthesia, the device was calibrated and then prepared to give quadruple stimulation at a frequency of 2 Hz every 12 seconds (sec). Fentanyl 1 mg/kg IV has been applied 3 min before induction. Induction was performed with propofol 2 mg/kg IV, and anaesthesia maintenance was provided with 1.5% isoflurane+50% N_2O+50% O_2. The patients were divided into three separate groups according to the dose of cis-atracurium used. 0.15 mg/kg was defined as Group 1, 0.20 mg/kg as Group 2, and 0.40 mg/kg as Group 3. The study participants were allocated to groups using the simple randomization method of sealed envelopes. Pre-operative patients were instructed to select one of the envelopes containing a group number. Cis-atracurium was administered based on the group number written inside the selected envelope. Endotracheal intubation was performed at 120 sec after neuromuscular agent application.

In the evaluation of intubation quality, the scoring system suggested by Aldrete et al.[11] was used. The intubation quality scoring tagging system is demonstrated in Table 1.

Heart rate per minute, ECG, and noninvasive pressure measurements monitored systolic and diastolic blood pressures. These hemodynamic data were recorded in the preoperative period, at the 1st, 5th, 15th, 25th, 35th and 55th minutes.

The time until 96% block developed following the administration of the muscle relaxant using the neuromuscular monitor was considered as the onset of effect time and was defined as T0 (sec). The time until 25% of the block was removed was considered the clinical effect time and was defined as T25 (min). The time until 75% of the block was removed was defined as T75 (min). The time from T25 to T75 was accepted as the recovery index and was defined as T25-75 (min).

Post-anaesthetic recovery (PAR) scoring was used to evaluate patient recovery.[11] Patients were evaluated and recorded with PAR scoring 10 min after extubation. The PAR scoring system is shared in detail in Table 2.

Table 1. Intubation quality scoring

Laryngoscopy	Vocal cords	Cough	Total score
Smooth (1)	Open (l)	None (l)	Excellent (3-4)
Medium difficulty (2)	Mobile (2)	Diaphragm movement (2)	Good (5-7)
Difficult (3)	Half sealed (3)	Straining (3)	Poor (8-10)
Impassable (4)	Fully sealed (4)	Severe cough (4)	Impassable (11-12)

Table 2. Post anaesthetic recovery (PAR) scoring		
Activity	a) The patient can move his four extremities voluntarily or on command b) The patient can move both extremities voluntarily or on command c) The patient cannot move his extremities voluntarily or on command	2 1 0
Respiratory	a) The patient can breathe deeply and cough. b) The patient is breathing intermittently or is dyspneic c) Patient is apneic	2 1 0
Circulation	a) Blood pressure is 20% different from pre-anesthesia value b) Blood pressure varies 20-50% from pre-anesthesia value c) Blood pressure is 50% different from pre-anesthesia value	2 1 0
Consciousness	a) The patient is awake b) The patient can be awakened by verbal stimuli c) Patient unresponsive to stimuli	2 1 0
Colour	a) Pink b) Pale yellow c) Cyanotic	2 1 0

Outcome

The primary outcome measure was the association of three different doses of cis-atracurium with the quality of endotracheal intubation. The secondary outcome measure was the relationship of three different doses of cis-atracurium with the duration of neuromuscular blockade and haemodynamic parameters.

Statistical Analysis

SPSS 22.0 package program was used to analyze the collected data statistically. Categorical variables were defined as number (n) and percentage (%). Continuous variables were described as mean, standard deviation, and minimum-maximum. The suitability of the variables to normal distribution was examined with the Kolmogorov-Smirnov/Shapiro-Wilk Test. The Chi-square and Fisher's Exact Test were used to compare categorical variables. Student-T test was used in groups with normal distribution, and Mann Whitney U Test was used in groups with non-normal distribution. Friedman analysis of variance was used for intragroup comparisons, and one-way analysis of variance was used for intergroup comparisons. In statistical calculations, the $p<0.05$ result was considered significant.

RESULTS

There was no significant difference in age, weight, height and gender distribution between the patients in three groups formed by applying three distinct doses of cis-atracurium. The demographic data of the patients are shared in **Table 3**.

A statistically significant difference was found between the groups regarding intubation quality ($p<0.05$). Intubation quality scores of patients in group 3 were higher than those in groups 1 and 2. Intubation score distributions between groups are demonstrated in **Table 4**.

Table 4. Intubation score distributions between groups				
Intubation quality	**Excellent, n (%)**	**Good, n (%)**	**Avarege, n (%)**	**Poor, n (%)**
Group 1	7 (35%)	11 (55%)	2 (10%)	-
Group 2	8 (40%)	9 (45%)	2 (10%)	1 (5%)
Group 3	19 (95%)	1 (5%)	-	-

The statistical studies conducted among the three groups regarding hemodynamic data measured at the 1st, 5th, 15th, 25th, 35th and 55th min after induction showed no significant difference in heart rate and mean arterial pressures ($p>0.05$). Hemodynamic data changes within the group are demonstrated in **Table 5**. Hemodynamic data changes within the group are demonstrated in **Table 5**.

Neuromuscular measurements and PAR scores of the three groups are demonstrated in **Table 6**. While there was no significant difference in the onset of effect times between the 1st and 2nd groups ($p>0.05$), a significant difference was detected between the 3rd group and the other two groups ($p<0.05$). When T25 was evaluated, the duration of the 3rd group was found to be significantly longer than the other two groups ($p<0.05$); there was no significant difference between the 1st and 2nd groups ($p>0.05$). There was no significant difference between the groups regarding T75, T25-75 and PAR recovery scores ($p>0.05$).

Table 3. The demographic data of the patients				
	Group 1 (0.15)	**Group 2 (0.20)**	**Group 3 (0.40)**	**P value**
Number of Cases, n	20	20	20	
Gender (F/M), n	14/6	11/9	16/4	
Age (year), mean±SD	39.94±11.47	49.70±13.81	40.82±12.19	0.163
Weight (kg), mean±SD	73.17±13.53	73.23±11.30	63.94±11.12	0.065
Height (cm), mean±SD	163.64±7.05	163.29±8.18	159.41±7.32	0.073

Table 5. Heart rate and mean arterial pressure changes according to time points within the group

	Group 1 n=20	Group 2 n=20	Group 3 n=20
Heart rate			
Preoperative, mean±SD	83.42±9.29	74.66±6.85	88.50±12,43
Ind. after 1 min., mean±SD	85.15±7.22	72.94±9.87	88.35±20.82
Ind. after 5 min., mean±SD	83.26±9.17	76.77±9.82	87.00±19.82
Ind. after 15 min., mean±SD	81.10±10.10	74.00±10.15	87.90±15.35
Ind. after 25 min., mean±SD	84.73±7.06	74.44±10.78	85.80±16.24
Ind. after 35 min., mean±SD	81.36±9.82	73.00±8.31	83.90±15.79
Ind. after 55 min., mean±SD	81.68±11.04	77.77±9.50	87.70±16.25
Intragroup P value	0.815	0.429	0.867
Mean arterial pressure			
Preoperative, mean±SD	98.94±11.97	100.89±11.90	89.96±17.02
Ind. after 1 min., mean±SD	92.37±16.14	86.06±22.17	83.88±15.92
Ind. after 5 min., mean±SD	86.49±15.75	90.88±20.69	92.59±20.37
Ind. after 15 min., mean±SD	86.54±13.97	93.94±20.59	86.60±17.28
Ind. after 25 min., mean±SD	88.38±14.00	93.11±17.20	82.21±18.89
Ind. after 35 min., mean±SD	88.38±14.82	93.67±13.60	87.39±16.99
Ind. after 55 min., mean±SD	92.67±14.81	89.61±17.13	86.76±14.33
Intragroup P value	0.056	0.124	0.829

Ind.: induction

Table 6. Neuromuscular measurement comparisons between groups

Group	T0, mean±SD	T25, mean±SD	T75, mean±SD	T25-75, mean±SD	PAR, mean±SD
1	199.78±52.54	56.26±12.34	90.84±32.58	15.05±10.34	8.36±1.46
2	181.11±39.97	63.44±8.48	95.16±19.60	13.27±7.58	8.61±1.42
3	102.25±34.32	78.45±18.93	99.60±17.76	10.35±5.80	8.75±1.37

DISCUSSION

One of the crucial developments in anaesthesia practice is the effort to find a muscle relaxant with ideal properties. The ideal features expected from ideal muscle relaxants are that they have a short onset time and high effectiveness, provide an excellent and good intubation quality, have minimal side effects and no cumulative effect, have no pharmacologically active metabolites, and can be entirely antagonised by anticholinesterases. Unfortunately, none of the muscle relaxants introduced into clinical practice to date contain all of these features. Cis-atracurium is also a product of these studies carried out to achieve the optimal. Our study aimed to find the most appropriate dose for the properties sought in an effective muscle relaxant by comparing different doses of Cis-Atracurium.

Littlejohn et al.[12] where they used thiopental or propofol and fentanyl as induction agents in their study, displayed that excellent and/or good intubation conditions were achieved in 120 sec with a dose of 0.15 mg/kg cis-atracurium. Bluestein et al.[13] conducted a similar study using midazolam in induction and obtained excellent intubation conditions in 120 sec with a dose of 0.15 mg/kg cis-atracurium. The results obtained by these two researchers at a dose of 0.20 mg/kg differ. While Littlejohn rated the intubation conditions at 90 sec as good/average, Bluestein found them to be excellent/good. The difference between the intubation conditions in these two studies was attributed to Bluestein's use of midazolam in induction.[12-14] Schmautz,[15] another researcher who investigated the intubation conditions of cis-atracurium, also found the 0.20 mg/kg dose for 90 sec to be weaker. Schmautz and Littlejohn, whose study results were similar, did not apply midazolam in induction. When evaluating the intubation conditions of cis-atracurium, the common opinion of all researchers is that better intubation conditions are provided at higher doses. Although this feature is valid for all muscle relaxants, the point to be considered is the undesirable effects of increasing the dose. Therefore, in our study, we paid attention to this issue and investigated the doses of 0.15 mg/kg, 0.20 mg/kg and 0.40 mg/kg of cis-atracurium. When perfect and good intubation conditions were compared in our study in which we used propofol/fentanyl in induction, we did not find a statistically significant difference between all three dose groups ($p>0.05$). However, when we evaluated only perfect intubation conditions, we found the 0.40 mg/kg dose of cis-atracurium superior to the other two dose groups. The difference was statistically significant ($p<0.01$). At the dose of 0.40 mg/kg, perfect intubation conditions were achieved in almost all patients in 95% (19/20), while at the dose of 0.20 mg/kg, perfect intubation conditions were achieved in 40% (8/20), and at the dose of 0.15 mg/kg, perfect intubation conditions were achieved in 35% (7/20).

It has been reported that a complete block of the adductor pollicis muscle is not required to ensure good intubation conditions, and relaxation in the vocal cords occurs before.[16-18] Non-depolarising block is based on a dynamic balance in which acetylcholine and muscle relaxant molecules compete for binding sites on the receptor. Thus, the frequency of activation of receptors by acetylcholine decreases as the concentration of the muscle relaxant increases.[16] In the 3rd group, the onset of the effect was shorter compared to the other two groups, and the block in the vocal cords started earlier, ensuring that the intubation conditions were excellent in this group.

As with every newly introduced drug, many studies have been conducted to reveal the dose-dependent hemodynamic and side effect profile of cis-atracurium. In the clinical studies conducted by Bryson and Faulds,[19] they detected 0.4% bradycardia, 0.2% hypotension, 0.2% flushing, 0.2% bronchospasm and 0.1% rash, and reported no side effects above 1%.[19] In Lepage and Lien's[9,14] studies in adult patients under thiopental sodium / fentanyl / midazolam anaesthesia, there were no significant changes in mean arterial pressure and heart rate at doses up to 4 mg/kg. In Lien's[9] study, changes in mean arterial pressure and heart rate were observed to increase or decrease by 3%.[9] In their study on patients with coronary artery disease, Reich and Konstadt,[20] who investigated the hemodynamic effects of cis-atracurium, found a decrease of at most 20% in mean arterial pressure with cis-atracurium at doses of 0.1 and 0.3 mg/kg. In studies investigating the hemodynamic changes of cis-atracurium compared to vecuronium, no difference was found between both agents, and both drugs' hemodynamic stability was demonstrated.[21,22] According to Lepage and Lien,[9,14] benzylisoquinoline compounds, metabolites of cis-atracurium, cause mild to moderate hemodynamic changes through stimulation of histamine release. Cis-atracurium at doses of 4 mg/kg and lower does not cause a significant change in dose-related mean plasma histamine levels, although there is a considerable variation between patients. In a study by Lepage,[14] a significant increase in mean plasma histamine concentration was observed 2 min after rapid administration of cis-atracurium. Although a two-fold or more increase in histamine levels was observed at doses of 1-2 mg/kg, histamine-related clinical findings did not occur. Our study evaluated the average arterial pressures and heart rates of all three dose groups. No significant difference was detected either within or between groups. No clinical or hemodynamic changes due to histamine discharge were found in the patients of all 3 groups. Accordingly, when we evaluate it together with the results of previous studies on this subject, we see that the results of our study are compatible with the literature.

A common use of cis-atracurium is in intensive care patients. In the studies conducted by Meretoja et al.[23] no central nervous system-related side effects or cerebral excitation were observed in any patients who underwent elective surgery or were hospitalised in the intensive care unit and received cis-atracurium infusion.[24] In our study, no side effects identified in the literature were observed in any of the three groups.

Another research conducted on cis-atracurium measured and evaluated data on dose-dependent neuromuscular blockade.[7,14] According to Lepage and Belmont,[7,14] depending on the dose, the degree and duration of neuromuscular blockade increases while the period to onset of effect decreases. During barbiturate or propofol anaesthesia, 99-100% pulse suppression was achieved in 4.6-5.8 min with a 0.1 mg/kg dose. The results of numerous studies on this subject have shown that higher doses of cis-atracurium provide maximum suppression in a shorter time. 0.15 mg/kg in 2.4-3.7 min,[13,15,25] 0.20 mg/kg in 2.7-3.8 min,[7,13-15] 0.40 mg/kg in 1.9 min[7] achieving maximum suppression is the dose-response times observed in the literature. A different study on this subject was prepared by Sorooshian.[26] In this study, based on healthy adults, the time required for a maximum block with 0.1 mg/kg Cis-Atracurium is prolonged by 1 minute in elderly patients and patients with renal insufficiency. At the same time, it is shortened by 1 minute in patients with end-stage liver disease. However, the maximum block is not affected in any of these patients during general anaesthesia.[26] In our study, in which we compared the maximum effect duration and clinical effect duration in 3 different doses of cis-atracurium using the TOF-GUARD monitor, we found the maximum effect duration significantly shorter and the clinical effect duration significantly longer in the patients in the 3rd group compared to the other two groups. The results we reached are consistent with those found in previous dose studies on this subject. However, in one patient each in the 1st and 2nd groups, we had to apply additional muscle relaxants even though the TOF-GUARD monitor showed maximum suppression at the 20th and 25th min of the operation. We found the post-tetanic count (PTC) responses we measured before drug administration to be 6 for the patient in group 1 and 7 for the patient in group 2. Afterwards, the operation continued and was completed. In our study, we excluded these two patients' hemodynamic data and neuromuscular block values from our statistical evaluations. Additionally, these patients also underwent abdominal surgery. The patient in the first group was a female patient weighing 95 kg, and the patient in the second group was a female patient

weighing 110 kg. We believe that multifactorial factors such as failure to comply with cold chain rules in storing muscle relaxants, difficulty in surgical manipulation in overweight patients, especially in abdominal operations, and insufficient anaesthetic depth for the patient during maintenance of general anaesthesia caused this incident.

The shortening of the maximum effect time and the prolongation of the clinical effect of the muscle relaxant used in higher doses are due to the fact that it creates more molecular load at the neuromuscular junction, and thus, its concentration in the plasma and synaptic gap is higher.[27] As suggested by Bowman et al.[28] according to the mass effect law, diffusion to binding points occurs rapidly, and the rate of first block development is faster. In their studies, Belmont and Lepage[7,14] found the average recovery time of 25-75% to be 8-13 min in adults for 0.1 mg/kg cis-atracurium and showed that the recovery time between doses of 0.1-0.4 mg/kg was independent of the dose. In another article on recovery time and quality, Brandom[29] reported that when an overdose of cis-atracurium (0.86 mg/kg) was given to an infant, recovery occurred within 10-15 min. In our study, no significant difference was found between the groups when clinical recovery times were compared, and recovery occurred within 10-15 min in all patients. Recovery from anaesthesia occurs with the return of the effects of the anaesthetic drugs and techniques used, and, in addition to the patient's physical characteristics, factors such as premedication dose and elimination of volatile agents used to affect the quality of recovery. In our study, we monitored the patients taken to the recovery room with PAR scoring 10 min later. Since the premedication and anaesthetic techniques of the patients were kept standard, the prolonged effects of muscle relaxants and the characteristics of the patients were effective in our follow-up. No significant difference was found in terms of recovery quality in the patients of all 3 groups.

Limitations

Among the limitations of our study is that it is single-centred and has a limited number of patients. Although our patients had similar demographic characteristics, they were not a single surgical unit patient undergoing the same operation. Failure to perform a similar surgical procedure may affect the need for muscle relaxants. Patients were not classified according to the surgical procedure. Additionally, we excluded patients who required additional muscle relaxants during the operation. We did not take these into consideration. More extensive prospective observational studies are needed on this subject.

CONCLUSION

As a result, although the 0.15 and 0.20 mg/kg application doses of cis-atracurium provide the mediocre conditions expected from a muscle relaxant, the 0.40 mg/kg dose provides excellent intubation conditions at a high rate (95%), medium clinical effect duration, significant hemodynamic effects, and significant hemodynamic effects. It is the most appropriate dose for clinical use as it does not cause any alterations, does not cause any complications during the recovery period and does not cause any significant side effects.

ETHICAL DECLARATIONS

Ethics Committee Approval

Since the study was old, local ethics were taken from the Ministry of Health Ankara Training and Research Hospital Ethics Committee at that time and published as a thesis. However, the records could not be accessed due to changes in hospital data processing.

Informed Consent

In this study, each patient provided informed consent prior to participation.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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