Original Article

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Efficacy of Cis-atracurium vs Atracurium in Patients undergoing Abdominal Procedures: A Randomised Clinical Study

Anaesthesia Section

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ABSTRACT

Introduction: Cis-atracurium has a neuromuscular blocking capacity approximately three times that of atracurium besylate. The Effective Dose (ED) 95 of cis-atracurium is 0.04 mg/kg, while that of atracurium is 0.2 mg/kg. Cis-atracurium is preferred over atracurium due to the lack of histamine release, providing better cardiovascular stability. This study compares these two drugs in terms of haemodynamic parameters, neuromuscular blocking properties, intubating conditions, and safety profiles.

Aim: To assess the efficacy of atracurium and cis-atracurium from various perspectives, including neuromuscular blockade, haemodynamic stability, and safety profiles.

Materials and Methods: A double-blinded, randomised clinical study was conducted from January 2019 to October 2019 in Rajkot, Gujarat, India. Sixty patients undergoing abdominal surgeries under general anaesthesia were allocated to two groups. Group A received a loading dose of atracurium 0.5 mg/kg followed by a maintenance dose of 0.1 mg/kg, while Group B received a loading dose of cis-atracurium 0.2 mg/kg followed by a maintenance dose of 0.03 mg/kg. During the surgical procedure, parameters studied included neuromuscular blockade, hemodynamic changes, intubating conditions, and safety profiles in terms of complications. Student's t-test was used to analyse normally distributed continuous variables, and the chi-square test was used for qualitative variables.

Results: The demographic profiles were comparable in both groups in terms of age (p-value=0.800), sex (p-value=0.393), weight (p-value=0.101), and American Society of Anaesthesiologists (ASA) grading (p-value=0.509). A significant increase in heart rate (99.46±8.06 (/minute) vs. 91.66±9.11 (/minute)) and mean arterial blood pressure (104.44±10.16 (mm of Hg) vs. 93.4±12.77 (mm of Hg)) was noted post-intubation in Group A compared to Group B. Patients in Group A (3.5±0.62 minutes) had a faster onset of neuromuscular blockade compared to Group B (4.6±0.49 (minutes)), while the duration of action of the first loading dose and the 25% recovery time from the last supplemental dose was longer in Group B (52.86±5.18 minutes and 41.66±3.60 minutes) than in Group A (31.2±4.82 minutes and 20.86±4.37 minutes). Fewer patients experienced complications (hypotension, erythema of the skin) in Group A compared to Group B.

Conclusion: Cis-atracurium releases less histamine compared to atracurium and has a longer duration of action. Cis-atracurium can be a better alternative to atracurium as it offers better haemodynamic, neuromuscular, and safety profiles with similar intubating conditions.

Keywords: General anaesthesia, Haemodynamics, Histamine, Intubation, Muscle-relaxant

INTRODUCTION

General anaesthesia consists of five components: analgesia, amnesia, paralysis, hypnosis, and immobility [1]. The integration of neuromuscular blocking agents into anaesthetic practice marked a significant milestone in modern anaesthesia techniques [2]. The characteristics of an ideal neuromuscular blocking agent include a fast onset of action, minimal changes in haemodynamics, a brief duration of action, absence of residual paralysis, and the provision of optimal intubating conditions such as full jaw relaxation, clear visualisation of the vocal cords, and the absence of an intubation response. Non-depolarising Neuromuscular Blocking Agents (NMBA) vary in their pharmacokinetic and pharmacodynamic profiles [2,3]. Atracurium and Cis-atracurium belong to the benzylisoquinolone group, serving as intermediate-acting non-depolarising NMBAs [4].

Atracurium offers advantages such as spontaneous degradation and non-organ-dependent elimination; however, its histamine release and potential for haemodynamic instability may restrict its use in specific clinical scenarios [5]. Cis-atracurium besylate, previously known by its developmental code 51W89, is a bisbenzyl tetrahydroisoquinolone compound, representing the R-cis isomer of atracurium with a lower propensity for dose-dependent histamine release in humans [6-9]. It is metabolised by Hofmann elimination. Compared to atracurium, cis-atracurium is more potent, has a rapid onset, longer duration of action, and provides more effective, rapid neuromuscular blocking with a longer duration of action and stable haemodynamic conditions [10].

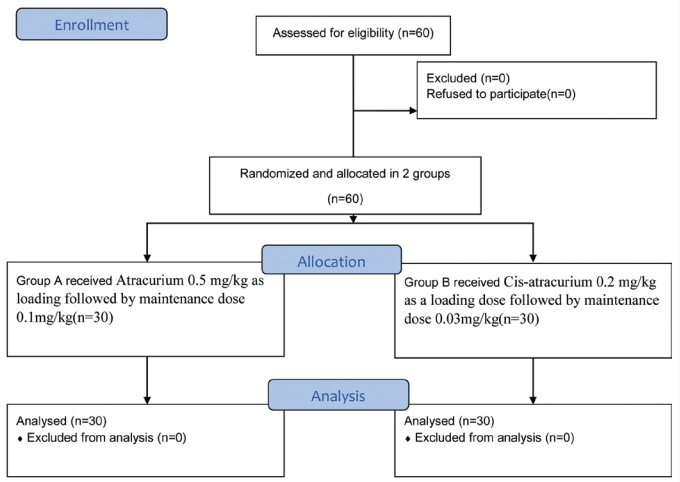
There are very few studies comparing atracurium and cis-atracurium regarding haemodynamic parameters, neuromuscular blocking properties, intubating conditions, and safety profiles [2,10,11]. Therefore, the authors have decided to conduct this study. The present study aims to compare and evaluate the effectiveness of both non-depolarising NMBDs from various perspectives, including neuromuscular blockade, haemodynamic stability, and safety profiles.

MATERIALS AND METHODS

A double-blinded, randomised clinical study was conducted on 60 patients from January 2019 to October 2019 at the Department of Anaesthesia, Pandit Dindayal Upadhyay Medical College and Hospital in Rajkot, Gujarat, India. The study was approved by the Institutional Ethics Committee (Regd. No.-ECR/635/INST/GJ 2014/RR-17), and written, informed consent was obtained from the patients. The study involved the participation of two investigators, with the first responsible for preparing and administering the drugs and the other entrusted with monitoring participants and collecting data while being blinded to the study. According to a previous study reference, in the atracurium group, the mean arterial blood pressure after the attempt of intubation was 91.6±6.4 mmHg, compared to 85.3±8.43 mmHg in the cis-atracurium group [10].

Sample size calculation: Assuming an 80% statistical power for the study, with 95% confidence (alpha=0.05), the sample size was calculated based on the presumption that cis-atracurium besylate

in the study group would have a beneficial effect compared to atracurium besylate. using the formula: 2 $(Z\alpha+Z\beta)^2*(SD)^2/(d)^2$, where d represents the median range and SD represents the standard deviation. Based on this formula, the sample size was determined to be 30. A total of 60 patients were equally and randomly divided into two groups using computer-generated randomisation [Table/Fig-1].



[Table/Fig-1]: CONSORT diagram.
Total participants N=60 patients

Group A received Atracurium besylate at a dose of 0.5 mg/kg ($2\times ED_{95}$) as a loading dose, followed by a maintenance dose of 0.1 mg/kg [12]. Group B received Cis-atracurium besylate at a dose of 0.2 mg/kg ($4\times ED_{95}$) as a loading dose, followed by a maintenance dose of 0.03 mg/kg [11].

Inclusion criteria: Patients of age group 18-65 years of either sex, ASA grade III, IV and V, the patients scheduled for abdominal surgeries under general anaesthesia and those anticipated duration of surgery of atleast one and a half hours are included in the study.

Exclusion criteria: Those patients taking medication known to interact with neuromuscular blocking agents, the patients with cardiac, renal, and hepatic impairment, neuromuscular system disorders, the pregnant and lactating women and those patients who refused to participate in the study were excluded.

Procedure

Pre-anaesthetic evaluation was conducted, and patients were asked to fast for eight hours before surgery. In the operating theatre, routine monitors such as Non Invasive Blood Pressure (NIBP), Saturation of Peripheral Oxygen (SpO_2), and Electrocardiography (ECG) were applied. A Peripheral Nerve Stimulator (PNS) (Fisher and Paykel HEALTHCARE, model number-INNERVTOR 272) was attached. An intravenous line was secured, and all patients received pre-medication with: Injection (Inj.) Glycopyrrolate 4 mcg/kg, Inj. Ondansetron 80 mcg/kg, Inj. Ranitidine 1 mg/kg intravenously. General anaesthesia was induced after pre-oxygenation with 100% O_2 for 3 minutes, using Inj. Fentanyl 1-2 mcg/kg and Inj. Propofol 2-2.5 mg/kg. The loading dose of the muscle relaxant was then administered to the patients according to their assigned group [13].

The onset time was measured from the administration of the muscle relaxant to the relaxation of the jaw. The end-point was a Train of Four (TOF) count of 0. The mean intubating condition was assessed based on the degree of jaw relaxation, ease of laryngoscopy, condition of the vocal cords, presence of coughing, and limb movements in response to intubation [Table/Fig-2] [14].

Anaesthesia was maintained with O_2+N_2O+Sevoflurane (1-2%) along with Atracurium besylate 0.1 mg/kg (Group-A) or Cis-atracurium besylate 0.03 mg/kg (Group-B) as a maintenance doses (top-up) based on the TOF ratio, along with assisted ventilation. Neuromuscular blockade was monitored every 5-10 minutes

Helbo-Hansen scoring system	Score			
	1	2	3	4
Jaw relaxation	Complete	Slight tone	Stiff	Rigid
Laryngoscopy	Easy	Fair	Difficult	Impossible
Vocal cords	Open	Moving	Closing	Closed
Coughing	None	Slight	Moderate	Severe
Limb movement	None	Slight	Moderate	Severe

[Table/Fig-2]: Grading of intubating condition score according to Helbo-Hansen scoring system (Steyn's modification [14].

after induction using a supramaximal stimulus (50 mA, 2Hz) by stimulating the ulnar nerve via surface electrodes. Post-tetanic count stimulation was utilised intraoperatively if the TOF ratio was deemed unsatisfactory. Patients were clinically monitored for any signs of histamine release until the end of the surgery. Continuous monitoring of haemodynamic parameters, including heart rate, mean arterial blood pressure, oxygen saturation, and end-tidal CO_2, was conducted. At the conclusion of the surgical procedure, patients were reversed with inj. neostigmine 50 mcg/kg and inj. glycopyrrolate. Extubation was performed once extubation criteria were met, with a TOF ratio of >0.9 [10]. Subsequently, patients were transferred to the recovery room for further observation.

Primary outcome: To compare atracurium besylate and cis-atracurium besylate in terms of onset, duration of action of the first loading dose, 25% recovery time from the last supplemental dose, intubating conditions, and recovery characteristics.

Secondary outcome: To evaluate the haemodynamic parameters after the administration of the loading dose and subsequent maintenance doses for both drugs.

To compare the safety profile of both drugs in terms of complications.

STATISTICAL ANALYSIS

The data from the study were compiled in Microsoft excel sheets, and statistical analysis was carried out using the Statistical Package for Social Science (SPSS version 20.0). Quantitative data were presented as mean±SD, while categorical data were expressed as numbers and percentages (%). The Student t-test was utilised to assess the significance of differences for quantitative variables (HR, BP), and the chi-square test was employed for qualitative variables. A p-value (probability value) of less than 0.05 was considered statistically significant.

RESULTS

[Table/Fig-3] displays the demographic data of the two groups, with values presented as mean and Standard Deviation (SD), and p-values obtained from the student t-test. A p-value greater than 0.05 is considered statistically non-significant.

		Group-A (n=30)	Group-B (n=30)	p-value
Age (years)	18-25	8	5	
	26-35	5	5	
	36-45	6	6	
	46-55	1	8	
	56-65	10	6	
Age (years) (Mean±SD)		42.63±16.85	43.66±14.54	0.8008
Sex (M/F)		19/11	20/10	0.3933
Weight (kg) (Mean±SD)		55.56±9.68	59.16± 6.85	0.1018
ASA grading (3/4/5)		14/13/3	13/16/1	0.509

[Table/Fig-3]: Demographic data.
ASA: American society of anaesthesiologists

[Table/Fig-4] illustrates the intraoperative Heart Rate (in minutes) of both groups at various intervals. The p-value is less than 0.05 after

intubation and at 5, 10, and 15 minutes post-intubation, indicating statistical significance.

Time (minute)	Mean±SD		p-value (Student's t-test)
	Group-A (n=30)	Group-B (n=30)	
Pre-induction (basal)	85.86±10.43	89.2±10.60	0.2236
Pre-intubation	85.86±10.58	89.2±9.43	0.2019
Post-intubation	99.46±8.06	91.66±9.11	**0.0009**
After 5 minutes	101.33±8.29	90.93±9.24	**0.0001**
After 10 minutes	96.13±8.88	90.86±10.56	**0.0048**
After 15 minutes	94.33±8.03	89.06±11.59	**0.0452**
After 30 minutes	87.06±7.97	87.93±9.84	0.7081
After 45 minutes	82.93±8.54	86±9.26	0.1871
After 60 minutes	81.6±8.60	85.4±7.70	0.0766

[Table/Fig-4]: Intraoperative heart rate (per minutes).

[Table/Fig-5] presents the intraoperative Mean Arterial Blood Pressure (MABP) (in mmHg) in both groups. The observations are comparable and statistically significant (p-value <0.05) after intubation and at 5, 10, and 15 minutes among the groups. However, there is no significant difference in MABP among the groups after 30, 45, and 60 minutes (p-value >0.05).

Time (mmHg)	Mean±SD		p-value (Student's t-test)
	Group-A (n=30)	Group-B (n=30)	
Pre-induction (basal)	97.73±12.65	95.02±12.31	0.4038
Pre-intubation	98.2±12.56	93.48±12.90	0.1564
Post-intubation	104.44±10.16	93.4±12.77	**0.0005**
After 5 minutes	104.6±12.35	92.06±12.60	**0.0003**
After 10 minutes	101.28±13.29	89.68±11.78	**0.0007**
After 15 minutes	96.06±10.61	88.48±10.13	**0.0064**
After 30 minutes	93.22±12.23	88.77±9.98	0.1280
After 45 minutes	89.42±9.77	86.46±9.13	0.2303
After 60 minutes	88.42±8.36	84.68±8.15	0.0846

[Table/Fig-5]: Intraoperative mean arterial blood pressure (mmHg).

The mean onset time of neuromuscular blockage in Group-A was lower compared to Group-B. The duration of action of the first loading dose and recovery time (25% recovery time) from the last supplemental dose was longer in Group-B compared to Group-A. These observations are statistically significant (p-value <0.05) as shown in [Table/Fig-6].

Neuromuscular monitoring	Mean±SD		p-value (Chi-square)
	Group-A (n=30)	Group-B (n=30)	
Onset time (minutes)	3.5±0.62	4.6±0.49	**0.0001**
Duration of action of 1st loading dose (minutes)	31.2±4.82	52.86±5.18	**0.0001**
Recovery time (25% recovery TOF) (minutes)	20.86±4.37	41.66±3.60	**0.0001**

[Table/Fig-6]: Neuromuscular monitoring (in minutes).

[Table/Fig-7] shows the intubating condition expressed as numbers and percentages. [Table/Fig-8] displays the intubating condition score in both groups, with results indicating no statistical significance (p-value >0.05). [Table/Fig-9,10] present SpO_2 and $EtCO_2$ in both groups, with p-values indicating statistical non-significance (>0.05).

Two patients in Group-A developed hypotension, and one patient developed erythema over the skin. No such complications were observed in Group-B.

DISCUSSION

Neuromuscular blocking agents are commonly used to induce muscle relaxation for facilitating tracheal intubation in patients undergoing surgeries under general anaesthesia [15]. When selecting a Neuromuscular Blocking Agent (NMBA) for tracheal intubation, an anaesthesiologist aims for key features including rapid onset, longer clinical duration of action, haemodynamic stability, and quick spontaneous reversal. A notable feature of atracurium and

		Group-A (n=30) (Number and %)	Group-B (n=30) (Number and %)
Jaw relaxation	Complete	27 (90%)	29 (96.67%)
	Slight tone	3 (10%)	1 (3.33%)
	Stiff	0	0
	Rigid	0	0
Laryngoscopy	Easy	30 (100%)	30 (100%)
	Fair	0	0
	Difficult	0	0
	Impossible	0	0
Vocal cords	Open	27 (90%)	28 (93.33%)
	Moving	3 (10%)	2 (6.67%)
	Closing	0	0
	Closed	0	0
Coughing	None	28 (93.33%)	29 (96.67%)
	Slight	2 (6.67%)	1 (3.33%)
	Moderate	0	0
	Severe	0	0
Limb movement	None	28 (93.33%)	29 (96.67%)
	Slight	2 (6.67%)	1 (3.33%)
	Moderate	0	0
	Severe	0	0

[Table/Fig-7]: Intubating condition. (Total N=30 patients).

	Mean±SD		p-value (Student's t-test)
	Group-A (n=30)	Group-B (n=30)	
Intubating condition score	5.33±0.71	5.16±0.53	0.2976

[Table/Fig-8]: Intubating condition score.

Time (minutes)	Group-A (Mean±SD)	Group-B (Mean±SD)	p-value (Student's t-test)
Pre-induction (basal)	97.8275862±0.778	97.758±1.382	0.809
Pre-intubation	97.8275862±0.734	98.275±0.573	**0.01**
Post-intubation	99.9310345±0.249	100±0	0.115
After 5 min	99.9655172±0.179	99.896±0.3	0.07
After 10 min	99.9655172±0.179	99.965±0.179	0.89
After 15 min	99.9655172±0.179	100±0	0.202
After 30 min	99.9655172±0.179	99.86±0.4	0.21
After 45 min	99.9655172±0.179	100±0	0.202
After 60 min	99.9655172±0.179	100±0	0.202

[Table/Fig-9]: SpO_2 monitoring.

Time (minutes)	Group-A Mean±SD	Group-B Mean±SD	p-value (Student's t-test)
Pre-induction (basal)	35.75±1.37	36.06±1.15	0.809
Pre-intubation	35.79±1.44	96.4±01.30	0.09
Post-intubation	38.20±1.98	38.66±2.481	0.43
After 5 min	37.05±1.40	38±1.63	0.20
After 10 min	38.89±1.68	38.2±1.86	0.133
After 15 min	37.86±1.58	37.36±1.779	0.202
After 30 min	37.65±2.30	37.13±1.82	0.33
After 45 min	39.58±1.95	39.03±1.63	0.20
After 60 min	40.62±2.60	41.5±1.56	0.16

[Table/Fig-10]: $EtCO_2$ monitoring.

cis-atracurium is their non-organ-dependent metabolism, making them advantageous for patients with compromised liver or kidney function. Cis-atracurium is believed to have several advantages over atracurium, including potentially releasing less histamine and having a longer duration of action [16].

The demographic profile of the present study participants were comparable in both groups. Heart rate increased immediately after intubation and at 5, 10, and 15 minutes post-intubation in both groups, with a greater increase in heart rate observed in Group-A compared to Group-B. These differences were statistically significant (p-value <0.05) as demonstrated in [Table/Fig-4]. Bohra P et al., conducted a comparative study of atracurium and cis-atracurium on the efficacy and safety of the intubating dose and found that heart rates were higher in Group-A compared to Group-C at 6, 8, 10, 15, 20, 25, 30, and 35 minutes, with the differences being statistically highly significant (p-value <0.001) [17].

The authors observed an increase in Mean Arterial Blood Pressure (MABP) in Group-A after intubation and at five and ten minutes post-intubation. However, there was a decrease in MABP at 30, 45, and 60 minutes compared to baseline MABP. On the other hand, in Group-B, there was no increase in MABP after intubation, and the patients remained haemodynamically stable. A decrease in MABP compared to baseline was observed at five, ten, fifteen, thirty, forty-five, and sixty minutes post-intubation. The results in the present study were statistically significant after intubation at 5, 10 and 15 minutes post-intubation, similar findings were seen in Mohanty AK et al., who studied Cis-atracurium in different doses versus Atracurium for thyroid surgery and found that Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and MABP increased after intubation and returned to baseline after 15 minutes [18]. A study by Jabalameli M et al., investigated the effect of cis-atracurium 0.15 mg/kg versus atracurium 0.5 mg/kg on intraocular pressure in patients undergoing tracheal intubation [19]. They observed a decrease in SBP, DBP, and HR after the administration of muscle relaxants, followed by an increase two minutes after intubation. SBP was significantly higher in the atracurium group compared with the cis-atracurium group.

In the present study, the mean onset time of neuromuscular blockade in Group-A was lower than in Group-B. The duration of action of the first loading dose was longer in Group-B compared to Group-A and was statistically significant (p-value <0.05). The recovery time (25% recovery time) from the last supplemental dose was much heigher in Group B as compared to Group A and the difference was statistically significant. A study by Bluestein L et al., observed that the onset time of neuromuscular blockade with cis-atracurium is shorter with higher doses [20]. Kale J et al., studied Atracurium and Cis-atracurium for the assessment of intubating conditions and found that the mean onset time for Group-A (3.7 minutes) was lower than Group-C (6.04 minutes) and the mean duration of action for Group-C was 59.43 minutes, whereas in Group-A it was 38.93 minutes, significantly longer, similar to the present study [21]. Athaluri VV et al., compared Atracurium versus Cis-atracurium and found that the mean onset of action was significantly faster in Group-B (cis-atracurium 0.15 mg/kg) compared to Group-B (cis-atracurium 0.1 mg/kg) and Group-A (atracurium 0.5 mg/kg) [22].

In the present study, the authors administered cis-atracurium at 4×ED95 and atracurium at 2×ED95. The Effective Dose 95 (ED95) is the dose required to produce 95% suppression of the muscle twitch response when used for intubation [23]. The ED95 dose of Cis-atracurium is 0.04 mg/kg (range 0.032-0.05 mg/kg) [9,24]. Previous studies have shown that four times the effective dose (4×ED95) and six times the effective dose (6×ED95) of cis-atracurium provide a more effective neuromuscular blockade and cardiovascular stability, but may result in a prolonged duration of action of the Neuromuscular Blocking Drug (NMBD) [10,25]. A study by El-Kasaby AM et al., concluded that only the six times ED95 dose of cis-atracurium produced a statistically significant difference compared to the dose of atracurium with excellent intubating conditions [10].

In terms of jaw relaxation, the authors observed complete jaw relaxation in 90% of patients and slight tone in 10% of patients in Group-A, while in Group-B, complete jaw relaxation was observed in 96.67% of patients and slight tone in 3.33% of patients. For laryngoscopy, the authors observed easy laryngoscopy in all patients (100%) in both groups. In terms of vocal cord visibility, here it was observed open vocal cords in 90% of patients and moving vocal cords in 10% of patients in Group-A, whereas in Group-B, open vocal cords were seen in 93.33% of patients and moving vocal cords in 6.67% of patients. There was statistically non-significant difference amongst the intubating score , being slightly heigher in Group A as compared to Group B. A study by Mohanty AK et al., also reported similar results to the present study when studying intubating conditions (Group-A: atracurium 0.5 mg/kg, Group-B: cis-atracurium 0.1 mg/kg, and Group-C: cis-atracurium 0.15 mg/kg) [18]. In the atracurium group, intubating conditions were excellent in 60% and good in 40% of patients, while in the cis-atracurium groups, it was 65% and 35%, and in Group-C, excellent intubating conditions were observed in 70% of patients and good in 30% of cases without a statistically significant difference. Subha PD et al., in her study, demonstrated that the intubation score used to assess tracheal intubating conditions was based on several factors such as the degree of jaw relaxation, movement of the vocal cords, and intubation response [26].

In Group-A, hypotension was observed in two patients and skin erythema in one patient, whereas in Group-B, no complications were observed among the patients. These adverse drug reactions were believed to be due to histamine release after the injection of atracurium besylate. Movafegh A et al., studied the prevalence of adverse drug reactions in both groups and found that despite more hypotension observed in the atracurium group, there was no statistical difference (p>0.05) [2]. According to authoritative drug references, both drugs have similar safety profiles. Similar to the present study, Bakhshi DR et al., in her study [11], found no signs of histamine release with the dose of cis-atracurium (0.2 mg/kg; 4×ED95), while skin rashes were found in two patients who received atracurium (0.5 mg/kg: 2×ED95).

Limitation(s)

The limitations of the present study were that it was conducted at a single center and involved doses of atracurium (2×ED95) and cis-atracurium (4×ED95). Multicenter studies with varying doses of atracurium and cis-atracurium could be conducted for different surgical procedures to obtain a more definitive conclusion. Plasma histamine levels were not measured due to the unavailability of this facility in our institute.

CONCLUSION(S)

The cis-atracurium besylate has better haemodynamic stability compared to atracurium besylate. Additionally, atracurium besylate has a faster onset of action compared to cis-atracurium besylate, but cis-atracurium besylate has a longer duration of action for both the first loading dose and supplemental dose compared to atracurium besylate. Both drugs have a similar profile in terms of intubating conditions after the injection of the first loading dose. Based on the above findings and results, it was concluded that cis-atracurium besylate could be a better alternative to atracurium besylate as it has a better haemodynamic, neuromuscular, and safety profile with similar intubating conditions.

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