RESEARCH ARTICLE

Effects of Atracurium and Cisatracurium on Pediatric Airway Pressure During Propofol Anesthesia

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Background: This study aimed to determine the effects of two muscle relaxants, i.e. atracurium and cisatracurium, on airway pressure of pediatric patients during general anesthesia maintained by propofol.

Methods: This double-blind clinical trial included 68 two-five-year-old candidates for elective lower abdominal surgeries under propofol anesthesia. The patients were randomized to two groups to receive either atracurium or cisatracurium as muscle relaxant. The changes in airway pressures were evaluated during the procedure.

Results: Peak airway pressure from the 10th to the 45th minutes and plateau airway pressure from the fifth to the 45th minutes after the induction of anesthesia were significantly lower in the cisatracurium group (P = 0.005). Four patients (11.8%) from the atracurium group developed laryngospasm. However, the two groups had no significant difference in this regard (P = 0.11).

Conclusion: Comparison of the two muscle relaxants showed that cisatracurium had lower peak and plateau airway pressure in pediatric patients under general anesthesia maintained by propofol.

Keywords: muscle relaxants; general anesthesia; atracurium; cis-atracurium

In pediatric surgery, general anesthesia usually requires endotracheal intubation. The choice of muscle relaxants to facilitate both endotracheal intubation and surgery [1] is generally based on different factors including the type of surgery, presence of underlying diseases, and airway status [2]. Atracurium and cisatracurium are common non-depolarizing muscle relaxants in pediatric surgery. The onset of effects and duration of action of atracurium are 3-5 and 25-35 minutes, respectively. Hofmann elimination and ester hydrolysis are used to eliminate these drugs from human body [3]. Cisatracurium, an isomer of atracurium, has an onset of effects of 3-5 minutes and a duration of action of 20-35 minutes [3]. Unlike its parent molecule, cisatracurium does not induce histamine release. Therefore, its rapid intravenous administration, even at high doses, will not lead to cardiovascular and pulmonary changes [3].

Due to the high risk of barotrauma and volutrauma in pediatric patients, appropriate selection and constant monitoring of ventilation parameters are critically important when using mechanical ventilation in pediatric surgeries under general anesthesia [4]. Bronchospasm, either induced by histamine or caused by intubation, increases airway resistance, decreases lung compliance, and ultimately elevates the risk of barotrauma and volutrauma [5-7].

As potent bronchodilators, volatile anesthetic agents can reduce the incidence or severity of bronchospasm and delay its onset [8-12]. However, following the growing application of intravenous anesthetic agents such as propofol [13-14], the mentioned advantage of volatile anesthetic agents is no longer usable. Higher severity of bronchospasm may therefore be observed during anesthesia. To the best of our knowledge, no research has evaluated the pulmonary changes caused by atracurium and cisatracurium during propofol-induced general anesthesia. The present study investigated the effects of these two agents on changes in airway pressure and lung compliance during pediatric surgery under propofol-induced general anesthesia.

Methods

This double-blind clinical trial was conducted in Imam Hossein Hospital (Isfahan, Iran) during 2015-16. The study population consisted of all candidates for lower abdominal surgery under general anesthesia. The inclusion criteria were age between two and five years, no history of pulmonary diseases or airway irritability, no history of upper respiratory tract infection during the two-week period before the surgery, no egg allergy, and no allergy to the mentioned agents. The patients were excluded if the duration of surgery exceeded 30 minutes. Cases of bronchospasm caused by factors other than the administered medications, severe bleeding (more than 10 ml/kg), intra-operative hypothermia (core temperature< 35 ºC), and difficult intubation were also excluded. The sample size in each group was calculated as 34 patients using the formula to determine the required sample size for the comparison of two means and a confidence interval of 95%, a power of 80%, the standard deviation of changes in airway pressure (estimated at 1.17),

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and the least significant difference of 0.8. The participants were recruited through convenience sampling.

Upon the approval of the medical ethics committee and receiving written informed consent from the parents, the eligible children were included and ordered to stay nil per os (NPO), six hours for two to three-year-old children, and eight hours for children older than three years of age. During NPO period, the patients received the 1.5-4.5 solution based on the 1-2-4 formula. The patients were premedicated with midazolam 0.1-0.3 mg/kg and sedated before being transferred to the operating room. During the operation, heart rate, blood pressure, arterial oxygen saturation (SpO2), core body temperature, and were measured and recorded as baseline values. The participants were then allocated to atracurium and cisatracurium groups using block randomization with block sizes of two and four. Another anesthetist, blinded to patient allocation, prepared the required medicine based on the number of patients in each block. The solutions were labeled as "A" or "B" and delivered to the researcher responsible for the conduct of the project.

After preoxygenation, anesthesia was induced by the administration of fentanyl 2 µg/kg and propofol 2 mg/kg. Atracurium (0.6 mg/kg) and cisatracurium (0.12 mg/kg) were used as muscle relaxants in the first and second groups, respectively. Ventilation with a mask and 100% oxygen was then performed for two minutes. Finally, the patients were intubated with an uncuffed endotracheal tube. The proper tube size was selected to ensure the absence of air leak at a pressure of 25 cm H2O.

Anesthesia was maintained with propofol 2-4 mg/kg plus 50% NO2-50% O2. Fentanyl 1 µg/kg was administered every 30 minutes to maintain analgesia during the surgery. At the end of the surgery, Prostigmin (neostigmine bromide) 40 µg/kg plus atropine 0.02 mg/kg was used to reverse the remaining effects of muscle relaxants. When the patient was fully awake and had normal number and depth of breath, extubation was performed and the child was transferred to the post-anesthesia care unit. Heart rate and SpO2 were monitored using electrocardiography and pulse oximetry, respectively. Mean arterial pressure (MAP) and axillary temperature were measured and recorded. Core body temperature was measured before the induction of anesthesia and every 15 minutes until the end of the surgery. End-tidal CO2 (ETCO2) was monitored using capnography. The ventilator of the anesthesia machine was used to measure the expiratory tidal volume, peak airway pressure, and plateau airway pressure every 15 minutes from the induction of anesthesia until extubation.

Dynamic and static lung compliance were calculated by dividing the expiratory tidal volume by peak and plateau airway pressure, respectively. The presence of any degree of wheezing was recorded as bronchospasm. The simultaneous incidence of respiratory obstruction and inspiratory/expiratory stridor and/or complete obstruction caused by spasm were regarded as signs of laryngospasm.

Chi-square and t-tests, along with repeated measures analysis of variance (ANOVA), were applied to analyze the collected data. All statistical analyses were performed using SPSS 24 (SPSS Inc., Chicago, IL, USA).

Results

Demographic data are indicated in (Table 1)

Table 1- Demographic characteristics of the two groups

Variable		Atracurium	Cisatracurium	P value
Age (months)		28.1 ± 13.7	29.9 ± 14.0	0.58
Weight (kg)		12.5 ± 2.9	13.4 ± 3.3	0.25
Gender	male	32 (94.1%)	30 (88.2%)	0.39
	female	2 (5.9%)	4 (11.8%)	

Table 2- The mean values of hemodynamic variables from the induction of anesthesia until the end of surgery in the atracurium and cisatracurium groups

Time	Heart rate (beats per second)			SPO2 (%)		
	Atracurium	Cisatracurium	P*	Atracurium	Cisatracurium	P*
Anesthesia induction	144.4 ± 19.1	145.1 ± 17.5	0.87	98.9 ± 1.5	98.9 ± 1.2	0.93
15th minute	15.5 ± 19.2	142.1 ± 15.9	0.43	99.4 ± 1.0	98.6 ± 1.7	0.042
30th minute	145.2 ± 17.2	140.7 ± 15.1	0.26	98.6 ± 1.7	99.6 ± 0.8	0.003
45th minute	144.6 ± 17.6	132.1 ± 30.5	0.13	98.3 ± 1.9	99.5 ± 0.7	0.009
P**	0.38			0.09		
Time	Mean blood pressure (mmHg)			ETCO2 (mmHg)		
	Atracurium	Cisatracurium	P*	Atracurium	Cisatracurium	P*
Anesthesia induction	71.1 ± 11.4	69.9 ± 10.5	0.64	37.0 ± 3.6	37.1 ± 3.0	0.91
15th minute	70.9 ± 11.8	66.2 ± 8.3	0.06	37.2 ± 3.9	35.4 ± 2.7	0.031
30th minute	71.6 ± 11.9	64.4 ± 7.2	0.004	37.3 ± 3.7	35.1 ± 2.5	0.005
45th minute	70.9 ± 11.7	64.7 ± 8.0	0.06	36.3 ± 3.2	34.7 ± 2.4	0.08
P**	0.22			0.15		

SpO2: Arterial oxygen saturation; ETCO2: End-tidal CO2

* T-test results for the difference between the two groups at any point of time

** The results of repeated measures analysis if variance for the trend if changes in the two groups

(Table 2) presents the mean values of hemodynamic parameters from the induction of anesthesia until the end of surgery (45th minute) in the two groups. Pairwise comparisons using t-tests revealed SpO2 at the 30th and 45th minutes and MAP at the 30th minute to be significantly higher in the cisatracurium group. ETCO2 was significantly higher in the atracurium group at the 15th and 30th minutes. However, repeated measures ANOVA showed that the trends of intraoperative changes in the mentioned variables were not significantly different between the two groups.

The mean values of the respiratory parameters of the two groups from the fifth until the 45th minute are summarized in (Table 3).

According to pairwise comparisons, there were significant differences in the peak airway pressure during the 10th-45th minutes and plateau airway pressure during the 5th-45th minutes between the two groups, i.e. patients receiving cisatracurium had significantly lower peak and plateau airway pressure. Moreover, repeated measures ANOVA confirmed the trends of changes in these two parameters to be significantly different between the two groups. However, the two groups had no significant differences in the expiratory tidal volume at any point of time. Likewise, the trend of changes in this parameter was not significantly different between the two groups.

While four atracurium recipients (11.8%) developed laryngospasm during the course of the study, no case of this complication was observed in the cisatracurium group. Nevertheless, the difference between the two groups was not significantly different based on Fisher's exact test results (P= 0.11). None of the patients in either the atracurium or cisatracurium group developed bronchospasm.

Table 3. The mean values of respiratory parameters from the induction of anesthesia until the end of the surgery in the atracurium and cisatracurium groups

Time (minute)	Peak airway pressure (cmH2O)			Plateau airway pressure (cmH2O)			Expiratory tidal volume (mm3)		
	Atracurium	Cisatracurium	P*	Atracurium	Cisatracurium	P*	Atracurium	Cisatracurium	P*
5th	14.3 ± 5.6	12.4 ± 1.0	0.06	11.4 ± 2.9	10.3 ± 0.9	0.04	120.6 ± 32.6	126.3 ± 31.7	0.47
10th	13.8 ± 3.3	11.8 ± 1.0	0.001	11.6 ± 3.0	9.9 ± 1.0	0.003	121.4 ± 30.0	1236.1 ± 32.0	0.54
15th	13.6 ± 2.9	11.7 ± 0.9	0.001	11.5 ± 2.5	9.7 ± 0.8	< 0.001	122/1±29/1	126±31/4	0/6
20th	13/9±3	11/6±0/9	< 0.001	11/4±2/5	9/5±0/7	< 0.001	121.6 ± 30.4	125.9 ± 30.9	0.57
25th	13.9 ± 2.9	11.6 ± 0.7	< 0.001	11.4 ± 2.6	9.5 ± 0.7	< 0.001	120.0 ± 29.7	125.5 ± 31.0	0.45
30th	13.9 ± 3.1	11.4 ± 0.7	< 0.001	11.2 ± 2.7	9.4 ± 0.6	< 0.001	119.6 ± 29.0	125.4 ± 31.5	0.43
35th	14.7 ± 3.9	11.4 ± 0.8	0.001	11.9 ± 3.4	9.4 ± 0.7	< 0.001	114.9 ± 24.0	121.9 ± 226.2	0.38
40th	14.6 ± 3.8	11.3 ± 0.6	0.001	11.7 ± 3.0	9.2 ± 0.8	0.001	114.3 ± 23.6	123.0 ± 27.2	0.28
45th	14.3 ± 3.6	11.3 ± 0.9	0.001	11.6 ± 3.2	9.3 ± 0.7	0.002	113.1 ± 23.7	123.1 ± 27.7	0.24
P**	0.005			0.007			0.3		

Discussion

Endotracheal intubation is a common procedure during general anesthesia. However, the high airway sensitivity in children turns this procedure into a major challenge in pediatric surgery. Therefore, several approaches have been developed to minimize spasm and prevent respiratory problems, especially during intubation. As a muscle relaxant, atracurium is widely used in the management of anesthesia in pediatric patients. Nevertheless, due to its ability to release histamine, atracurium can cause airway spasm and hypotension. This study, hence, compared the intra- and post-operative changes in respiratory parameters following the administration of atracurium and cisatracurium (which does not have a histamine-releasing effect).

Since the atracurium and cisatracurium recipients in this study had no significant differences in terms of demographic characteristics (e.g. age, sex distribution, and weight), these variables had no confounding effects on our findings. In other words, the observed differences between the two groups can be attributed to the type of muscle relaxant used.

According to the obtained results, although the two groups had significant differences in a number of hemodynamic parameters, such as SpO2, ETCO2, and MAP at some time points, they were not generally and significantly different in heart rate, blood pressure, SpO2, and ETCO2. As no cases of severe hemodynamic complications, e.g. severe increases or decreases in blood pressure and heart rate, were detected in wither group, both medicines can be safely administered in children.

Intraoperative evaluation of respiratory parameters indicated that the patients in the cisatracurium group had more desirable conditions than the atracurium group, i.e. the mean peak airway pressure and plateau airway pressure were lower in the cisatracurium group. Therefore, the risk of respiratory complications was lower in this group. Likewise, the mean ETCO2 level was lower in the cisatracurium group. However, the two groups had no significant difference in terms of expiratory tidal volume. In a study on the effects of cisatracurium and rocuronium on lung function in children, Yang et al. concluded that he clinical doses of both medicines caused slight changes in lung function which were nor clinically measurable. Meanwhile, subclinical comparison of the two agents showed that rocuronium caused greater spasm in small airways [8]. These results are in agreement with our findings.

In the current study, four patients from the atracurium group developed bronchospasm. No cases of bronchospasm or laryngospasm were seen among the cisatracurium group.

Bronchospasm during general anesthesia results in increased airway pressure, impaired ventilation, and even pulmonary barotrauma. These changes may impose greater risk on children who are generally more sensitive. Histamine release, induced by drugs used for the induction and maintenance of general anesthesia, particularly muscle relaxants, may be responsible for bronchospasm. Atracurium is an intermediate-duration muscle relaxant with minimal cardiovascular side effects. It does not require hepatic or renal elimination and is an appropriate choice for patients under general anesthesia. However, its administration can trigger histamine release and thus increase the risk of several complications including bronchospasm. Cisatracurium, on the other hand, does not cause histamine release.

Conclusion

Based on our findings, compared to atracurium, cisatracurium causes fewer respiratory complications during and after endotracheal intubation in pediatric patients under general anesthesia with propofol. This medicine is thus recommended as a suitable alternative to atracurium in children.

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