Drug Design, Development and Therapy

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ORIGINAL RESEARCH

Effects of Cisatracurium, Rocuronium, and Mivacurium on Intraocular Pressure During Induction of General Anesthesia in Ophthalmic Surgery

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy

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Objective: Maintaining intraocular pressure (IOP) is important in preventing ocular complications in patients undergoing ophthalmic surgery for general anesthesia. The effects of non-depolarizing neuromuscular blockers on IOP remain unclear. The present study compared the effects of cisatracurium, rocuronium, and mivacurium on IOP during induction of general anesthesia in vitreous retinal surgery.

Materials and Methods: In this prospective randomized double-blinded study, 133 patients undergoing vitreous retinal surgery were randomized into one of the three groups: Group cisatracurium (n=45), Group rocuronium (n=44), or Group mivacurium (n=44). Each drug (cisatracurium 0.1 mg kg^{-1} in Group cisatracurium, rocuronium 0.6 mg kg^{-1} in Group rocuronium, and mivacurium 0.2 mg kg^{-1} in Group mivacurium) was administered during induction of anesthesia. IOP and hemodynamic parameters were measured at 1 min before anesthesia induction (T0). Bispectral index (BIS) was maintained between 45 and 55 after propofol administration (T1). Train-of-four stimulation (TOF) was below 0 after muscle relaxant administration (T2) and after laryngeal mask implantation (T3).

Results: Both ipsi-operative and control-operative IOP at T1, T2, and T3 significantly decreased from the baseline values (T0) in all three groups ($P<0.05$). The IOP changes between T1 and T2 among three groups were similar ($P>0.05$). The values of systolic blood pressure (SBP) and diastolic blood pressure (DBP) at T1 and T2 significantly decreased in all three groups compared to T0 ($P<0.05$).

Conclusion: Bilateral IOP significantly decreased from the baseline values in all three groups during the induction phase. Cisatracurium, rocuronium, and mivacurium did not induce significant changes in bilateral IOP.

Keywords: intraocular pressure, cisatracurium, rocuronium, mivacurium, general anesthesia, ophthalmic surgery

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Introduction

During the general anesthesia of ophthalmic surgery, especially in the induction phase, it is vital to control the IOP effectively.[1,2] Anesthesia drugs and procedures may cause fluctuation of intraocular pressure (IOP), which has adverse effects on the prognosis of ophthalmic patients.[3,4] A large number of studies have confirmed that intravenous general anesthetic agents, such as propofol, usually directly or indirectly reduce IOP.[5–7]

The effects of neuromuscular blockers on IOP remain unclear. While succinylcholine used in the induction of anesthesia is known to cause an increase in IOP,[8,9]

there is no consensus regarding the effects of non-depolarizing neuromuscular blockers on IOP. Several randomized studies have shown that IOP decreases after administration of cisatracurium.[10,11] Rocuronium has been shown to cause a decrease in IOP during induction of anesthesia.[9,12] However, another study indicated that rocuronium did not cause as high an increase in IOP as succinylcholine with rapid sequence induction of anesthesia using propofol and fentanyl.[13] Thus far, there is sparse published report showed that mivacurium decreased IOP and the greatest decrease was reached five minutes after bolus.[14] Furthermore, there is also a study that demonstrated that mivacurium had negative effects on IOP and OPA (ocular pulse amplitude).[15]

This is the first study to compare the effects of cisatracurium, rocuronium, and mivacurium on IOP and hemodynamic changes associated with induction of general anesthesia in ophthalmic surgery.

Methods

Ethics

Ethical approval for this study (approval #2017030) was provided by the Institution Review Board of the Eye & ENT Hospital, Fudan University (Chairperson: Dr Fanglu Chi) on 24 May 2017.

This randomized, double-blind, prospective study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants. The trial was also registered before patient enrollment at Chinese Clinical Trial Registry (Clinical Trial Number: ChiCTR-IPD-17012514).

Protocol

One hundred and thirty-five patients undergoing vitreous retinal surgery from 1 September 2017 to 30 July 2018 in the Eye & ENT Hospital, Fudan University were enrolled in this study. We included patients aged between 18 and 65 years. Patients were classified as class Ⅰ, Ⅱ, or Ⅲ according to American Society of Anesthesiologists (ASA). Exclusion criteria included ocular trauma, glaucoma, pregnancy, neuromuscular disorders, receiving medicine known to interfere with neuromuscular function, allergy to the study drugs. Patients were randomized into one of the three groups: Cisatracurium Group: cisatracurium 0.1 mg/kg (SHANGHAI PHARMA; Shanghai, China), Rocuronium Group: rocuronium 0.6 mg/kg (N.V. Organon; The Netherlands, Germany), Mivacurium Group: mivacurium 0.2 mg/kg (THE WELLCOME FOUNDATION LIMITED; MIDDLESEX, UK).

All patients fasted for more than 8 h. Electrocardiography, pulse oximetry, non-invasive blood pressure, and capnography were recorded in the operating room. After preoxygenation for 3 mins, anesthesia was induced using target-controlled infusion of propofol. When bispectral index (BIS) was maintained between 45 and 55, 0.1 mg/kg cisatracurium, 0.6 mg/kg rocuronium, or 0.2 mg/kg mivacurium were given, respectively. After train-of-four stimulation (TOF) value reduced to 0, laryngeal mask airway was inserted. Then, 2 ug/kg fentanyl was given and mechanical ventilation was performed. General anesthesia was maintained by 0.9–1.1 minimum alveolar concentration sevoflurane and 50% air in oxygen with a constant fresh gas flow of 2 L/min.

Data Collection

Age, sex, BMI, ASA, and operative time were recorded. All patients received topical anesthesia with two conjunctival drops of 0.4% oxybuprocaine before measurement. Ipsi-operative IOP, control-operative IOP, HR, Systolic blood pressure (SBP), and Diastolic blood pressure (DBP) were got at the following points: 1 min before anesthesia induction (T0), when BIS was maintained between 45 and 55 after propofol administration (T1), when TOF was below 0 after muscle relaxant administration (T2), and after laryngeal mask implantation (T3). IOP was measured using Tono-Pen AVIA (Reichert, USA) by an ophthalmologist who was blinded to grouping. The recovery time of spontaneous breathing (time from discontinuation of anesthetics to spontaneous breathing), the extubation time (time from discontinuation of anesthetics to extubation), the awakening time, and the recovery time of myodynamia were recorded for all patients.

Statistical Analysis

The main efficacy endpoint of our study was ipsi-operative IOP when TOF was below 0 after muscle relaxant administration (T2). Based on the data of the pilot study (13.2±4.5 mmHg in Group cisatracurium, 15.5±6.48 mmHg in Group rocuronium, 16.0±5.6 mmHg in Group mivacurium, 8 patients in each group), the sample size of 40 patients in each group was calculated at α=0.05, β=0.2 with the sample size software (NCSS-PASS, Kaysville, UT, USA). We expanded the sample size in each group to 45 patients to allow for loss to follow-up. Using SPSS 23.0 software (SPSS Inc., Chicago, Il) to perform analysis for data. Continuously, normally distributed data were presented as

Table 1 Patients Demographic Data

	Patients	Gender (M/F)	Age (Yr)	ASA (I/II/III)	BMI (kg/m^2)
Group cisatracurium	45	19/26	45.04±13.79	23/21/1	23.59±3.21
Group rocuronium	44	25/19	41.11±12.85	27/17/0	25.27±5.46
Group mivacurium	44	24/20	44.43±15.01	22/22/0	23.40±3.07

Note: Data are shown as means ± SD.
Abbreviation: ASA, American Society of Anesthesiologists; BMI, body mass index.

mean±SD. ANOVA was performed to analyze the difference among three groups and paired samples *t*-test was used to compare IOP, HR, SBP, and DBP between preinduction (T0) and postinduction (T1, T2, T3) within the group. Categorical data were analyzed by the chi-square test. $P<0.05$ was considered statistically significant.

Results

Among 135 patients recruited, two patients (one patient in Group rocuronium and one patient in Group mivacurium) were excluded because they were not cooperative to measure IOP before anesthesia induction. We analysed data from 133 patients (Group cisatracurium, n=45; Group rocuronium, n=44; Group mivacurium, n=44). There were no significant differences among the three groups with respect to sex, age, ASA classification, BMI, duration of surgery (Table 1).

As shown in Figure 1, both ipsi-operative and control-operative IOP at T1, T2, T3 significantly decreased from the baseline values (T0) in all three groups ($P<0.05$). The IOP changes between T1 and T2 among the three groups were similar ($P>0.05$) (Table 2). As shown in Table 3, the values of SBP and DBP at T1, T2 significantly decreased in all three groups compared to T0 ($P<0.05$); SBP at T3 in Group cisatracurium and Group mivacurium significantly decreased from T0 ($P<0.05$); DBP at T3 in Group mivacurium significantly decreased from T0 ($P<0.05$); HR at T1 in Group mivacurium, at T2 in Group rocuronium and at T3 in Group cisatracurium and Group rocuronium decreased from T0 ($P<0.05$).

Among all three groups, there were no significant differences in duration of surgery, the recovery time of spontaneous breathing, the extubation time, the awakening time, and the recovery time of myodynamia ($P>0.05$) (Table 4).

Discussion

The aim of the present study was to evaluate and compare the effects of cisatracurium, rocuronium, and mivacurium on IOP in patients undergoing ophthalmic surgery with general anesthesia. Bilateral IOP significantly decreased from the baseline values in all three groups during the induction phase. We found that administration of the three non-depolarizing neuromuscular agents was not associated with significant changes of bilateral IOP.

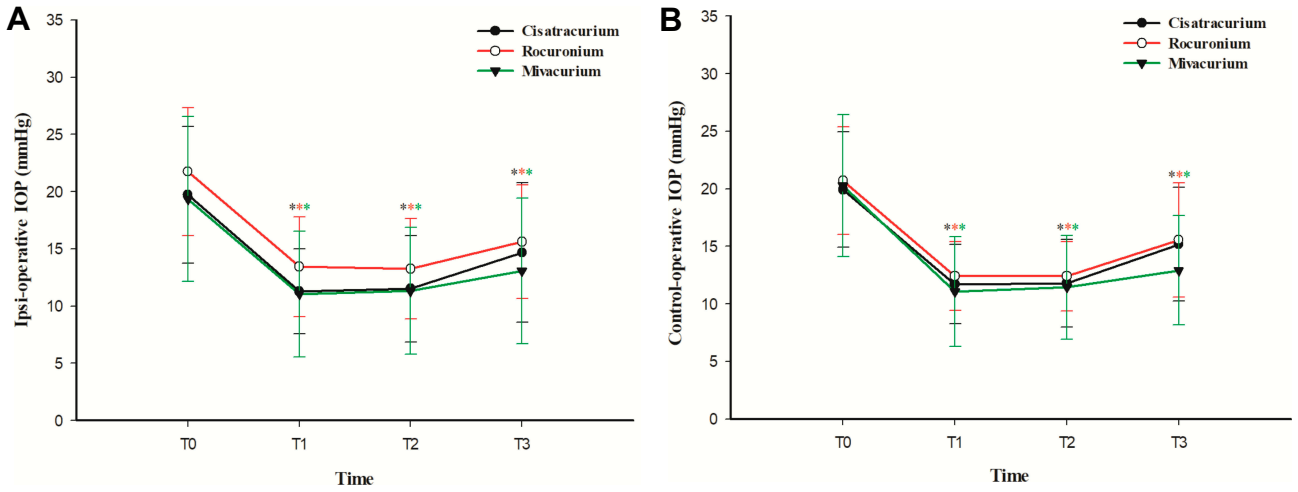

Figure 1 The ipsi-operative (**A**) and control-operative IOP (**B**) at T0, T1, T2, T3 in three groups.T0: 1 min before anesthesia induction; T1: when BIS was below 40; T2: when TOF was below 0%; T3: after laryngeal mask implantation. * Significance difference in comparison with T0 ($P<0.05$).

Table 2 The IOP Changes Between T1 and T2

	Groups	T1–T2(x±s)	F value	P value
Ipsi-operative IOP	Group cisatracurium	−0.22±16.21	0.473	0.624
(mmHg)	Group rocuronium	0.20±14.18		
	Group mivacurium	−0.27±8.58		
Control-operative IOP	Group cisatracurium	−0.07±11.39	0.203	0.817
(mmHg)	Group rocuronium	0.00±15.59		
	Group mivacurium	−0.39±18.12		

Notes: Data are shown as means ± SD. T1: when BIS was below 40; T2: when TOF was below 0%.

Table 3 Hemodynamic Change in 3 Groups

	Groups	T0(x±s)	T1(x±s)	T2(x±s)	T3(x±s)
HR	Group cisatracurium	80.04±11.71	78.07±14.50	77.47±10.11	83.89±13.73*
(beats/min)	Group rocuronium	77.5±13.57	77.02±14.87	84.43±14.03*	92.45±13.82*
	Group mivacurium	78.16±17.65	83.57±12.79*	79.09±13.39	81.45±13.95
SBP	Group cisatracurium	140.36±22.31	103.62±11.28*	110.36±14.28*	130.11±24.75*
(mmHg)	Group rocuronium	143.07±23.11	109.52±15.64*	121.02±19.48*	138.36±28.23
	Group mivacurium	139.14±23.20	93.98±15.59*	106.77±18.08*	119.02±20.83*
DBP	Group cisatracurium	85.16±10.43	65.22±9.40*	69.16±11.99*	82.13±17.38
(mmHg)	Group rocuronium	86.89±13.92	66.77±10.38*	75.52±15.19*	87.91±19.80
	Group mivacurium	83.39±13.74	57.80±12.51*	65.68±11.24*	75.41±14.55*

Notes: Data are shown as means ± SD. T0: 1 min before anesthesia induction; T1: when BIS was below 40; T2: when TOF was below 0%; T3: after laryngeal mask implantation. *Significance difference in comparison with T0 ($P<0.05$).
Abbreviations: IOP, intraocular pressure; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

The normal range of IOP is 10–22 mmHg (mean 15 mmHg) and value more than 24 mmHg is pathologic.[9] As patients undergoing vitreous retinal surgery, the baseline IOP values of partial patients among the three groups in this study were greater than 24 mmHg. During the general anesthesia of ophthalmic surgery, especially in the induction process, it is vital to control the IOP effectively because the elevation of IOP can induce adverse prognosis of ophthalmic patients.[16] For the anesthetic induction of ophthalmic surgery, IOP can be affected by different general anesthetic agents, blood pressure, vomiting, coughing, pressure from masks, laryngoscopy, and endotracheal intubation.[17] In our study, none of the patients experienced IOP values greater than 24 mmHg at any of the collected times of measurement.

After administration of propofol, both ipsi-operative and control-operative IOP at T1 (when BIS was below 40) significantly decreased from the baseline values in all three groups in this study. Without combination with other intravenous agents, the phenomenon of this decrease mainly reflected the IOP lowering effect of propofol. The IOP decreasing effect of propofol in the present research is consistent with previous studies.[18] The effect of propofol on the IOP may be caused by the reduction of aqueous humor production.[19] Moreover, increase outflow of the aqueous humor could also contribute to the IOP decreasement.[20] Additionally, hemodynamic response associated with propofol could also reduce IOP at some degree.[7]

In this study, both ipsi-operative and control-operative IOP at T2 (when TOF was below 0%) significantly decreased from the baseline values in all three groups. However, comparing with the IOP value at T1 (when BIS was below 40), there was no significant change after administration of cisatracurium, rocuronium, and mivacurium. Additionally, the IOP changes between T1 and T2 among the three groups

Table 4 Multiple Comparisons of Recovery Times in PACU

	Operation Time (Min)	Recovery Time of Spontaneous Breathing (Min)	Extubation Time (min)	Awakening Time (min)	Recovery Time of Myodynamia (min)
Group cisatracurium	83.13±43.43	16.33±8.27	21.96±7.91	23.13±8.35	25.78±9.14
Group rocuronium	72.61±44.16	18.48±9.91	25.50±11.11	25.84±10.98	28.52±10.82
Group mivacurium	79.93±51.34	17.36±8.50	24.25±8.16	24.89±8.42	28.34±10.62

Note: Data are shown as means ± SD.

were similar. The results of this study indicated that cisatracurium, rocuronium, and mivacurium did not affect the IOP in patients undergoing ophthalmic surgery.

Several randomized studies have shown that IOP decreases after administration of cisatracurium in sedated patients or in patients undergoing tracheal intubation.[10,11] Rocuronium has been shown to cause a decrease in IOP during induction of anesthesia.[9,12] On the contrary, there is also a study indicated that rocuronium did not cause as high an increase in IOP as succinylcholine with rapid sequence induction of anesthesia using propofol and fentanyl.[13] The effects of mivacurium on IOP also remain unclear.[14,15] Discrepancy in results between our study and previous researches may be due to differences in methodologies, including combination of induction drugs, dose, and anesthesia procedures. None of the significance on IOP between T1 and T2 among three groups was caused by three non-depolarizing neuromuscular agents because the results were isolated from effects of propofol.

Several limitations should be noted in the interpretation of our research. First, as a kind of anesthesia procedure to help ventilate, placement of facemask may cause fluctuation of IOP. However, we did not measure the IOP during the protocol because we considered it would disturb effective ventilation. Second, we used propofol as an induction agent making it challenging to differentiate the effects of the non-depolarizing neuromuscular agents on IOP from the hemodynamic and ocular hypotensive effects of propofol. In the future, thiopental may be a good alternative to minimize the hemodynamic and the ocular hypotensive effects of the induction agents.[21]

In conclusion, administration of cisatracurium, rocuronium, and mivacurium does not produce changes on IOP in patients undergoing ophthalmic surgery with general anesthesia. Therefore, cisatracurium, rocuronium, and mivacurium can be safely used in ophthalmic surgeries.

Data Sharing Statement

We are willing to share all relevant data in this study. After the article is published, readers can contact the corresponding author to obtain data by email. The study protocol, statistical analysis plan, and clinical study report will also be available.

Acknowledgments

Assistance with the study: none. Financial support and sponsorship: Shanghai Committee of Science and Technology, China (Grant No.16DZ1911108). Presentation: none.

Disclosure

The authors report no conflicts of interest in this work.

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