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Comparison of Effects of Oral Ivabradine and Oral Clonidine as Premedicants on Intraocular Pressure Changes Following Intubation with Succinylcholine

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Abstract

Background: Endotracheal intubation done with succinylcholine raises intraocular pressure which can be of significance in cases of traumatic open globe injury. *Aims:* The study was done to compare the efficacy of oral Ivabradine and Clonidine in lowering the intraocular pressure rise following intubation using succinylcholine. *Methods:* A total of 105 patients were enrolled. Three groups having 35 patients each were formed. Group I: Received oral Ivabradine 5 mg, Group II: Received oral Clonidine 0.1 mg & Group III received placebo one hour before intubation. Intraocular Pressure (IOP) was measured with schiotz tonometer preoperatively & at various intervals to assess the effect of clonidine and Ivabradine on IOP. *Results*: A total of 105 pateints were enrolled. Three groups having 35 patients each were formed. The mean IOP of the patients from 3 groups were comparable initially (p - 0.082). At all later time points, the mean IOP of patients from 3 groups was statistically different ($p < 0.001$). The mean IOP in patients who received clonidine was significantly lesser as compared to control group at all time points except at the baseline ($p < 0.001$). However, among patients who received Ivabradine, the mean IOP was significantly less than the control group only at T1, and T7. *Conclusions*: Oral Clonidine can be recommended as premedicant for obtunding the rise in IOP following endotracheal intubation using succinylcholine. Oral Ivabradine showed no effect on IOP during endotracheal intubation using succinylcholine.

Keywords: Clonidine; Ivabradine; Succinylcholine; Intraocular pressure.

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Introduction

Laryngoscopy contribute significantly to hemodynamic changes like increased heart rate, elevated systolic blood pressure, and cardiac arrhythmias along with increase in Intraocular Pressure (IOP).[1]

General anesthetics and nondepolarizing neuromuscular blocking drugs usually reduce IOP whereas studies have shown that succinylcholine increase IOP.[2] It has been found that IOP of 25 mm Hg or more is considered pathological. Some studies have shown transient elevation of IOP 2–4 minutes

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after IV injection of succinylcholine.[3] Increase in IOP is of clinical significance in setting of open eye injury. Clonidine is an alpha-2 adrenergic agonist with antiischemic activities[4,5] whereas Ivabradine controls heart rate.[6]

The present study was conducted to study the efficacy of oral Ivabradine and Clonidine in lowering the intraocular pressure rise following intubation using succinylcholine as a muscle relaxant.

Materials and Methods

This prospective, randomized study was conducted at a tertiary referral hospital for a duration of one year after obtaining approval from the hospital ethical committee and patients' written informed consent.

Sample size

We hypothesized that Clonidine and Ivabradine will decrease the IOP after IV injection of succinylcholine. For the calculation of sample size for this trial, the pooled standard deviation of IOP was taken as 2.8 mm Hg[7] and minimum detectable difference (effect size) of IOP was assumed to be 1.25 mm Hg. Assuming alpha error as 5%, power as 80%, and attrition rate as 10%, the sample size for each group was calculated as 35.

Adult patients aged between 18 and 50 years belonging to ASA Grade I and II, undergoing general anesthesia, were included in the study. Patient's refusal, patients with ocular diseases, patients with cardiovascular diseases and history of hypertension, pregnant and breast feeding females, patients with difficult airway, with Hepatic/renal impairment, in whom the study drugs were contraindicated and obese patients (BMI more than 30) were considered as exclusion criteria. Randomization, blinding and allocation concealment: Randomization of the participants was done using computer-generated random sequences into Test Groups or Control Group. The person allocating the treatment to the included participants was not aware of the randomization sequence as it was distributed in the sealed envelope.

To ensure blinding, the Test Groups as well as Control Groups were not informed regarding the drug which they were being given and the drugs were as identical as possible to avoid ascertainment bias. To ensure blinding, the assessor also was not aware of the treatment provided to the patient.

Group-I (Test Group): Received oral Ivabradine, 5 mg tab one hour before intubation,

Group II (Test Group): Received oral Clonidine 0.1 mg tab one hour before intubation,

Group-III (Control Group): Received placebo one hour before intubation.

Preanesthetic check-up and routine investigations like complete blood count, serum creatinine, chest *X*-ray & Electrocardiogram (ECG) were done. Patients were kept nil by mouth for 8 hours. Intraocular pressure was recorded in both eyes after instilling 2 drops of 4% Lignocaine in each eye, using schiotz tonometer under supervision of an ophthalmologist in the preop period just before administration of test/placebo drug which is given 1 hour prior to intubation.

Intravenous cannulation was done with 18G cannula and ringer lactate solution was started in preoperative room. After shifting the patient to the operation theatre all the standard monitorings were applied. IOP and other parameters were recorded just before premedication. Inj. Midazolam 0.07 mg/kg and Inj. Ondansetron 0.12 mg/kgwas given as premedicant intravenously just before induction.

All patients were given general anesthesia according to the standard protocol. The patient was induced by Inj. Propofol (2 mg/kg body weight) & intubation was facilitated using Inj. Succinylcholine 2 mg/kg intravenously. Intubation was achieved with an appropriate size oral cuffed, endotracheal tube by the aid of Macintosh laryngoscope blade. Intubation was performed by an experienced anesthesiologist in each case. After securing the airway, intraocular pressure was recorded in both eyes at set intervals by an Ophthalmologist. Difficult airway cart was ready for patients with difficult airway. Any patient where prolonged laryngoscopy of more than 60 second was done was excluded from the study. Surgery was not allowed to commence till the recordings were completed which was ten minutes in each case.

Anesthesia was maintained with 40:60 of oxygennitrous oxide mixture with 1% isoflurane and intermittent doses of vecuronium bromide. Extubation was performed, after reversing the neuromuscular blockade with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg, following thorough oral suctioning. All the patients were followed in the postoperative room for the next 3 hours for any complications like dizziness, deep sedation and bradycardia.

The IOP recordings were noted at various intervals. T0 - Preoperatively - just before administration of the study drug, T1 - Just before premedication inside OT, T2 - Just after intubation,

T3 - 1 minute after intubation, T4 - 3 minutes after intubation, T5 - 5 minutes after intubation, T6 - 8 minutes after intubation, T7 - 10 minutes after intubation.

Each patient was examined clinically and all parameters were recorded on a separate case record form and thereafter, entered on a Microsoft excel sheet for statistical analysis.

Statistical analysis

The statistical analysis was done using SPSS 17 (Armonk, NY: IBM Corp). The categorical variables are presented as percentages and continuous variables were presented as mean (SD) or median (IQR) as applicable. For the comparison of categorical variables, Chi-square test was used. For comparison of more than 2 means, ANOVA (Analysis of variance) was used. p - value of < 0.05 was considered statistically significant.

Results

The study was conducted over a period of one year from May 2016 to April 2017. Data from 105 patients was analyzed in this study. There was no significant difference in the demographic profile of the three groups with respect to age, sex, nutritional status and ASA status, (Fig. 1).

Systolic blood pressure was recorded at various time intervals in all the three groups and was not found to be statistically significant except at T2, (Fig. 2).

Difference in heart rate of patients of three groups was not found to be statistically significant at baseline (T0). Thereafter, at all the periods of observation from T1–T7 mean heart rate of patients of Group III were found to be significantly higher than that of Group I and Group II, (Fig. 3).

In Group I, change in baseline IOP was found to be statistically significant at all the periods of observation except at T6 (p = 0.064). In Group II, change in baseline IOP was found to be statistically significant only at T1, T6 and T7. In Group III, change in baseline IOP was found to be statistically significant at all the periods of observation except at T6 (p = 0.169) and T7 (p = 0.147), (Table 1).

Mean IOP of patients of Group III was found to be statistically significant only at T1, T3, T4 and T7. Mean IOP of patients of Group III was found to be statistically higher than that of Group II at all the periods of observation except at T0, (Table 1).

Difference in IOP among patients of three groups at T0 was not found to be statistically significant. At T1 mean IOP of patients of Group III (14.47 ±

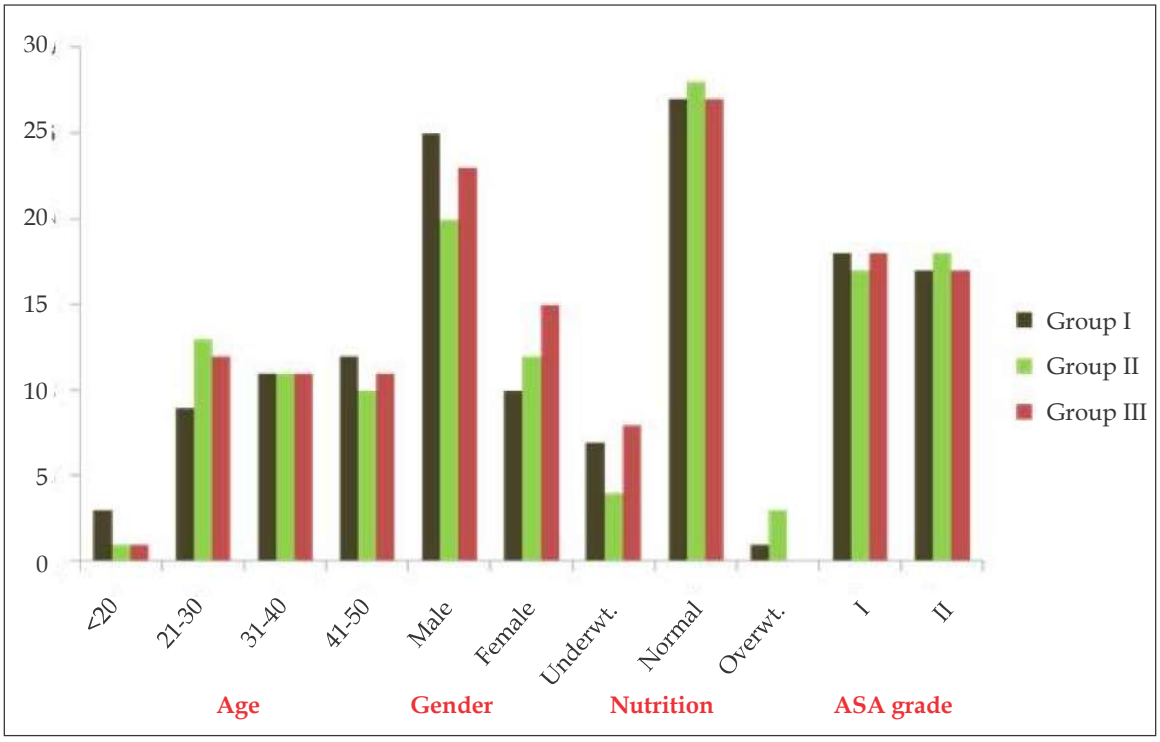

Fig. 1: Comparison of Demographic data between the study groups

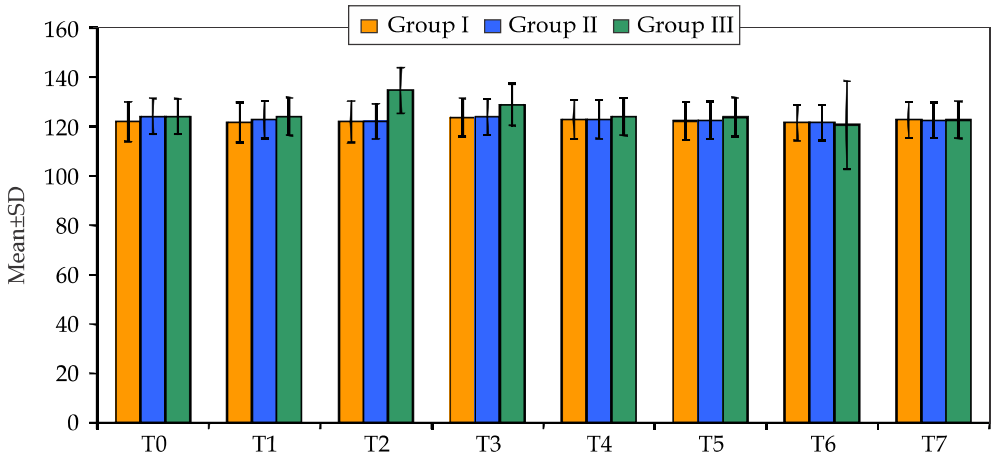

Fig. 2: Comparison of Systolic blood pressure between groups at various time interval

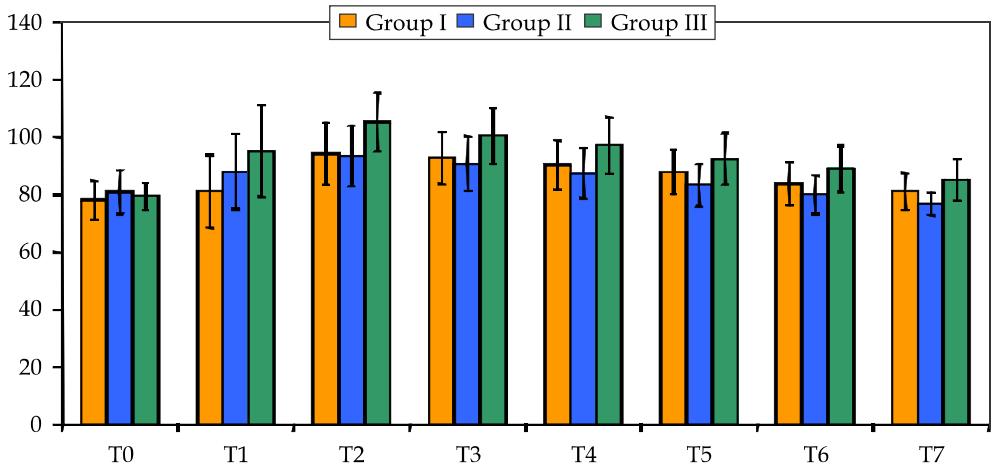

Fig. 3 : Comparison of Heart rate between groups at various time interval

Table 1: Intragroup Change in Baseline Mean IOP at different time intervals

	Group I					Group II					Group III				
	Mn ch.	**SD**	**% ch.**	**'t'**	**'p'**	**Mn ch.**	**SD**	**% ch.**	**'t'**	***'p'***	**Mn ch.**	**SD**	**% ch.**	**'t'**	***'p'***
T1	-1.04	0.35	-7.99	-17.58	<0.001	-0.29	0.46	-2.14	-3.688	0.001	0.84	0.54	6.18	9.247	<0.001
T2	2.39	1.36	18.27	10.37	<0.001	0.34	1.45	2.56	1.395	0.172	2.39	0.76	17.50	18.616	<0.001
T3	1.96	1.24	14.99	9.301	<0.001	0.17	1.50	1.28	0.674	0.505	2.23	1.10	16.35	11.981	<0.001
T4	1.50	1.08	11.49	8.233	<0.001	0.06	1.53	0.43	0.221	0.827	1.69	1.18	12.37	8.434	<0.001
T5	1.39	1.03	10.61	7.962	<0.001	-0.29	1.47	-2.14	-1.152	0.257	1.16	1.08	8.49	6.360	<0.001
T6	0.31	0.97	2.41	1.915	0.064	-0.63	1.33	-4.70	-2.795	0.008	0.31	1.32	2.31	1.405	0.169
T7	-0.86	0.48	-6.56	-10.60	<0.001	-1.26	1.42	-9.40	-5.233	<0.001	-0.34	1.37	-2.52	-1.486	0.147

Table 2: Inter Group Comparison of Mean IOP at different time intervals

	Group I Vs Group II			Group I Vs Group III			Group II Vs Group III		
	Mean diff.	**SE**	***'p'***	**Mean diff.**	**SE**	***'p'***	**Mean diff.**	**SE**	***'p'***
T0	-0.31	0.25	0.431	-0.57	0.25	0.066	-0.26	0.25	0.568
T1	-1.07	0.26	<0.001	-2.46	0.26	<0.001	-1.39	0.26	<0.001
T2	1.73	0.36	<0.001	-0.57	0.36	0.264	-2.30	0.36	<0.001
T3	1.47	0.34	<0.001	-0.84	0.34	0.040	-2.31	0.34	<0.001
T4	1.13	0.32	0.002	-0.76	0.32	0.048	-1.89	0.32	<0.001
T5	1.36	0.25	<0.001	-0.34	0.25	0.372	-1.70	0.25	<0.001
T6	0.63	0.24	0.028	-0.57	0.24	0.051	-1.20	0.24	<0.001
T7	0.09	0.16	0.853	-1.09	0.16	<0.001	-1.17	0.16	<0.001

1.23 mm Hg) was found to be significantly higher as compared to Group I (12.01 ± 0.08 mm Hg) and Group II (13.09 ± 1.46 mm Hg). At T2 difference in mean IOP of patients was found to be statistically significant between Group I and II and Group II and III. Difference in mean IOP of patients of three groups were found to be statistically significant at all the periods of observation from T3–T7, (Table 2).

No complication like dizziness, deep sedation and bradycardia was observed in any of the patients in the postoperative room during the 3 hours observation period.

Discussion

Patient with difficult airway who require tracheal intubation in cases of open globe injury often require succinylcholine to facilitate intubation, Succinylcholine is also one of the commonly used muscle relaxants during rapid sequence induction and intubation which is often done in trauma patients as they are considered full stomach. Succinylcholine produces an undesirable rise in intraocular pressure which may prove disastrous in patients with penetrating eye injuries.

Intraocular Pressure (IOP), in normal conditions, ranges from 12 to 20 mm Hg which is influenced by several factors such as central venous pressure, choroidal blood volume changes, and extraocular muscle tonicity. Sudden increase in blood pressure, as occurs after laryngoscopy and endotracheal intubation, results in the choroidal blood volume increase and eventually a 10 to 20 mm Hg increase in IOP. This increase in IOP can be troublesome during ophthalmic surgeries, especially in the presence of glaucoma or open eye trauma. Increase in (IOP) following endotracheal intubation during general anesthesia is commonly reported as a side effect while using depolarizing muscle relaxant, Succinylcholine.

Lignocaine, Diazepam, other previously studied drugs and substitution of nondepolarizing drugs of intermediate duration like Atracurium[8] or rocuronium[9] for succinylcholine have all been ineffective with inconsistent results. In the recent year's alpha-adrenergic agonist like Clonidine have shown a considerable attenuating effect on hemodynamic rise including intraocular pressure.[10] Recently, Ivabradine, a novel sinus node inhibitor, has shown attenuating effects for hemodynamic with promising ability and with minimal side effects.[11]

Ivabradine binds to hyperpolarization voltage-gated channels which carry the I (h) current in the eye, leading to transient, dose-dependent changes of the electroretinogram.[12] Considering the promising hemodynamic effect of Ivabradine, we were encouraged to evaluate its impact on rise of intraocular pressure among patients scheduled to undergo laryngoscopy and endotracheal intubation under succinylcholine. For a reference, Clonidine, one of the premedication that has proven attenuating effect on pressor response following laryngoscopy and endotracheal intubation, was used.

The major outcome of present study was the difference in IOP between baseline value and just before premedication value. Ivabradine showed a 7.99% decline in IOP while Clonidine showed a 2.14% decline during the period. Thus, both the trial drugs indicated an onset of IOP attenuating effect before intubation itself. However, during the same period, in placebo group an IOP increase of 6.18% was observed. While the reductions in IOP in both the trial groups could be attributed to the attenuating effect of the drugs, the increase in IOP in placebo group can be attributed to a psychological stress and anxiety among patients undergoing surgery. Presence of preoperative anxiety and its hemodynamic effect has been recorded in several studies previously[13–15] and use of some antianxiety drugs or nonpharmacological management modalities is advised in some instances.[16–18] In present study, no such intervention to tackle the anxiety/stress induced IOP rise was done between preoperative IOP assessment and just before induction period. The findings in turn suggest that patients having premedication of either of two drugs may have a positive impact on the anxiety-stress related hemodynamic changes too.

In present study, following intubation an increase of 18.27% and 17.50% in IOP was observed in Ivabradine and placebo groups, however, Clonidine showed an increase of 2.56% only. Thus, showing that premedication with Ivabradine did not help to attenuate the intraocular pressure rise following intubation. Interestingly during the entire observation period (up to 10 minutes after intubation), the IOP values were minimum in Clonidine group as compared to placebo and ivabradine groups. Despite having mean IOP values much below the placebo group just after premedication inside OT (T1), Ivabradine had significantly lower mean IOP as compared to placebo only at 3 out of six postintubation observations. Thus, indicating that at the given dose of 5 mg oral premedication, Ivabradine was only marginally

better than placebo. However, Clonidine was able to attenuate the IOP rise effectively. Although, IOP rise following intubation can be as high as 10–20 mm Hg[19] however, no such increase was observed in present study in any of the study groups.

The present study showed the efficacy of clonidine in controlling the IOP rise following intubation. As far as effect of Ivabradine on IOP was concerned, the present study failed to elucidate the same. Ivabradine despite showing a higher reduction in IOP between premedication to preintubation period failed to exercise the IOP attenuating effect. This could be attributed probably to a shorter half-life of the drug. It is pertinent to mention here that Clonidine has almost 3–12 times longer half-life as compared to that of Ivabradine. Similarly, bioavailability of Clonidine is also almost 1.5 times higher as compared to Ivabradine. The initial better attenuation of IOP in Ivabradine group (between premedication and preintubation interval) could be attributable to the faster onset of the drug. As such it is difficult to comment on the optimal dosage of the drug as we used 5 mg drug only which is the minimum dose available commercially. It might be possible that higher dosages may provide a better outcome. For this interventions using variable dosages of Ivabradine are recommended. Though there are a number of studies supporting the role of Clonidine premedication in maintenance of hemodynamic stability among patients undergoing endotracheal intubation[20,21] there are limited studies regarding the role of clonidine and ivabradine in the maintenance of IOP.

Although the primary objective of the study was to evaluate and compare the attenuation of IOP rise following endotracheal intubation between oral Clonidine and ivabradine premedication groups, during the course of study, we felt that IOP rise to succinylcholine intubation did not reach to a considerably high level to need any particular intervention even in placebo group, that means, that among patients with baseline IOP in normal range, IOP rise following intubation does not hold much value. On reviewing the previous studies too, we did not find that during endotracheal intubation period there was any considerable and substantial rise in IOP, however, during postoperative period within 24 hours, some studies have reported considerable rise in IOP 5–6 hours after the surgery, hence, whether premedication for IOP attenuation during endotracheal intubation is required among patients having normal IOP at baseline itself requires a reconsideration.

Further studies with variable drug-dose combinations are recommended to find the optimal dose of ivabradine required to control IOP similar to the effect produced by oral clonidine 0.1 mg.

Conclusion

Based on the outcome of the present study, we conclude that oral Clonidine (0.1 mg) can effectively be recommended as premedicant for obtunding the rise in IOP following endotracheal intubation after administration of succinylcholine. Oral Ivabradine, 5 mg do not prevent increase in IOP following intubation with succinylcholine.

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