EFFECTIVENESS OF ORAL IVABRADINE AND ORAL CLONIDINE AS PRE MEDICATIONS ON INTRAOCULAR PRESSURE CHANGES FOLLOWING INTUBATION WITH SUCCINYLCHOLINE: A COMPARATIVE STUDY

Pragati Garg *, Sanjay Chaubey **, Mahrukh Khan **,1 and Asim Ahmad **

* AIIMS, Raebareli, ** ELMCH, Lucknow.

ABSTRACT

Purpose: Endotracheal intubation with succinylcholine causes an undesirable rise in IOP. Clonidine, a selective alpha 2 agonist, reduces IOP and provide better hemodynamic stability. Ivabradine, a sinus node inhibitor, shows attenuating effects for hemodynamics. This study aims to compare the effectiveness of both these drugs as premeditats on IOP changes post-intubation with succinylcholine

Methods: A hospital-based analytical comparative study was done on 105 patients aged 18-50 years scheduled for elective surgeries under general anaesthesia. The patients were randomly allocated into three groups of 35 each by computer-generated randomized tables. Group I was given oral ivabradine, Group II was given oral clonidine, and Group III received a placebo 1 hour before intubation. IOP was measured just before premedication (T0), just before intubation (T1), just after induction of anaesthesia (T2), 2 minutes after intubation (T3), 5 minutes after intubation (T4), 8 minutes after intubation (T5), 10 minutes after intubation (T6). P<0.05 was taken as a significant value.

Results: The study findings showed that in comparison to ivabradine and placebo, clonidine was able to significantly decrease the IOP after intubation with succinylcholine (p<0.001). The range of IOP rise from baseline IOP to IOP following intubation was very less with clonidine administration in comparison to ivabradine and the placebo group. The result was statistically significant at all periods of time when the IOP was measured after intubation (p<0.001).

Conclusion: Oral clonidine can effectively and safely be recommended as a premedicate for reducing the rise in IOP following endotracheal intubation with succinylcholine.

KEYWORDS intraocular pressure (IOP), clonidine, ivabradine

Introduction

Endotracheal intubation is one of the commonly performed procedures in elective and emergency surgeries [1]. Intubation leads to stimulation of the sympathetic nervous system, which causes hemodynamic changes like increase in heart rate, increase in systolic blood pressure & cardiac arrhythmias [2]. It is also associated with increased intraocular pressure (IOP) mainly due to increased ocular blood flow [2].

Succinylcholine – A depolarizing muscle relaxant, transiently elevates IOP2-4 minutes after IV Injection, further aggravated by endotracheal intubation [3]. Clonidine is an imidazoline derivative, selective central α2 agonist with analgesic, anti-anxiety and sedative effects[4]. It is confirmed that clonidine effectively decreases the anaesthetic drug requirements and neuroendocrine responses to stressors and stimulations[5,6]. It can effectively reduce intraocular pressure and provide better hemodynamic stability[5,6]. Recently, ivabradine, a novel sinus node inhibitor, has shown attenuating effects for hemodynamics with the promising ability and minimal side effects[7].
In the present study, we tried to evaluate the efficacy of oral ivabradine and clonidine in lowering the intraocular pressure rise following intubation using succinylcholine as a muscle relaxant.

**Materials and methods**

The present study was conducted in a tertiary hospital with the collaboration of an ophthalmologist and an anesthesiologist. 105 adult patients in the age group 18-50 years scheduled for elective surgeries under general anaesthesia, ASA grade I and II physical status (I am normal healthy patient: II is patient with mild systemic disease) were enrolled for the study after proper ethical clearance and informed consent of the patient. Patients with the ocular disease with or without increased IOP; those with history of any hepatic /renal impairment, hypertension, heart rate <60 beats per minute, systolic blood pressure <100mmhg and those with ECG abnormalities were excluded from the study.

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The patients were randomly allocated into three groups of 35 each according to the computer-generated randomized tables. Group I was given oral ivabradine 5mg tablet 1 hour before intubation. Group II was given oral clonidine 0.1 mg tablet 1 hour before intubation. Group III received a placebo 1 hour before intubation. Group III received a placebo 1 hour before intubation. Group I was given oral ivabradine 5mg tablet 1 hour before intubation. Group II was given oral clonidine 0.1 mg tablet 1 hour before intubation. Group III received a placebo 1 hour before intubation. Group I was given oral ivabradine 5mg tablet 1 hour before intubation. Group II was given oral clonidine 0.1 mg tablet 1 hour before intubation. Group III received a placebo 1 hour before intubation.

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Preoperative baseline intraocular pressure (IOP) was measured after instillation of 4% Lignocaine drops in the right eye by applanation tonometer. Intraocular pressure was recorded in the right eye just before premedication (T0), just before intubation inside OT (T1), just after induction of anaesthesia (T2), 2 minutes after intubation (T3), 5 minutes after intubation (T4), 8 minutes after intubation (T5), 10 minutes after intubation (T6).

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Data so obtained were subjected to statistical analysis using SPSS software version 15.0. Results obtained were analyzed statistically by the “t” test, paired and unpaired. P<0.05 was taken as a significant value.

**Results**

This study was done on 105 adult patients in the age group of 18-50 years scheduled for elective surgery under general anaesthesia after the informed consent and ethical clearance. The patients were randomly allocated into three groups of 35 each according to the computer-generated randomized tables. Group I was given oral ivabradine 5mg tablet 1 hour before intubation. Group II was given oral clonidine 0.1 mg tablet 1 hour before intubation. Group III received a placebo 1 hour before intubation.

The Mean age of patients in group I was higher than group II and group III. The majority of patients were females in all the groups. Statistically, the difference in age and sex among different groups was insignificant. All the patients in both groups were ASA Grade I/II. (Table 1)

The intergroup comparison of mean intraocular pressure at the various time was assessed (Table 2). The baseline IOP of group III patients was higher at all time intervals, including the baseline values compared to group I and group II. However, on comparing group I and group II we found that the IOP was more in group II patients (T0-T1). Subsequently, there was a fall in IOP at all time intervals following intubation (T2-T6) in group II subjects. Differences in mean IOP of patients of the above three groups were statistically significant at all the periods of observation from T1-T6.

Intergroup comparison of Mean IOP at different time intervals reported that the mean IOP of group 1 patients was lower than group II at T0 and T1. However, the difference in IOP of patients of both groups was statistically significant only at T1. Mean IOP after all the time intervals from T2-T6 was higher in Group I individuals as compared to group 2, and the difference in IOP was significant at all time intervals except at T6. (Table 3)

The patients in group III had higher mean IOP at all intervals as compared to that of Group I, and the difference was statistically significant only at T1.

The mean IOP of group III patients was higher than group II at all intervals, and the difference was significant at all intervals except T0.

Comparing the percentage change in IOP in all three groups (Table 4), we found that maximum change in IOP was observed just after the intubation. In contrast, minimum change was seen 10 minutes after intubation (T6). Change in IOP was statistically significant at all then periods except at T6.

In group 2, the maximum change in IOP was observed at 10 minutes post-intubation while minimum change was observed at T4, i.e. 5 minutes after intubation. Change in IOP was statistically significant only at T1 and T6.

In group 3, maximum change was observed after intubation (T2), while the minimum change was 10 minutes (T6). Change in baseline IOP was statistically significant at all observation periods except at T1 and T6.

**Discussion**

Intraocular pressure is influenced by central venous pressure, ocular flow and extraocular muscle tonicity[8]—intubation results in increased choroidal blood volume and eventually a rise in IOP[8]. A rise in IOP after intubation is commonly seen using depolarizing muscle relaxants like succinylcholine.

Succinylcholine is the most commonly used muscle relaxant in rapid sequence induction because of its fast onset and short duration of action when given in the recommended 1.5 mg/kg IV. dose. However, it can have serious side effects[9]. Though it remains the relaxant of choice in non-fasting patients, succinylcholine produces an undesirable rise in IOP[9].

Ghai et al. (2001)29 evaluated the intraocular pressure and hemodynamic changes after laryngeal mask airway and endotracheal tube[10]. 50 adult patients planned for surgery under general anaesthesia were the study participants. They found a statistically significant increase in heart rate, systolic blood pressure, diastolic blood pressure and intraocular pressure in both the groups after insertion of laryngeal mask airway or endotracheal tube[10]. Transient IOP elevation after IV succinylcholine injection may lead to adverse outcomes.

Several studies have been performed to assess the effectiveness of some drugs as pre-medicines on reducing IOP and providing better hemodynamic stability. Low dose oral clonidine
### Table 1 Demographic profile of study groups.

| Age  | Total (N=105) | Group I (n=35) | Group II (n=35) | Group III (n=35) |
|------|---------------|---------------|----------------|-----------------|
|      | No. | %   | No. | %   | No. | %   |
| ≤20  | 5   | 5.71%| 1   | 2.86%| 1   | 2.86%|
| 21-30| 34  | 34.29%| 13  | 37.14%| 12  | 34.29%|
| 31-40| 34  | 34.29%| 11  | 31.43%| 11  | 31.43%|
| 41-50| 32  | 31.43%| 10  | 28.57%| 11  | 31.43%|

\[ \chi^2 = 2.486 \ (df = 6); \ p = 0.870 \]

| Mean ± SD | 35.01 ± 9.02 | 35.69 ± 9.50 | 34.77 ± 8.34 |
|-----------|-------------|-------------|-------------|
| Female    | 68          | 25          | 23          |
| Male      | 37          | 10          | 12          |

\[ \chi^2 = 1.586 \ (df = 2); \ p = 0.453 \]

### Table 2 Intergroup comparison of Mean IOP at different time intervals.

| Time | Group I | Group II | Group III | ANOVA |
|------|---------|----------|-----------|-------|
|      | Mn     | SD       | Mn        | SD    | Mn       | SD      | F   | P     |
| T0   | 13.471 | .5131    | 13.734    | 1.4824| 14.243   | 1.2195  | 4.090| .020  |
| T1   | 12.200 | .0000    | 13.311    | 1.5105| 15.037   | 1.2095  | 57.308| .000  |
| T2   | 15.843 | 1.3705   | 14.071    | 1.9757| 16.420   | 1.2776  | 21.213| .000  |
| T3   | 15.423 | 1.0376   | 13.554    | 2.0237| 16.206   | 1.0887  | 27.375| .000  |
| T4   | 14.954 | 1.0345   | 13.751    | 2.0140| 15.511   | 1.0157  | 13.797| .000  |
| T5   | 14.803 | .9183    | 14.803    | .9183 | 15.249   | .8448   | 23.943| .000  |
| T6   | 13.614 | 1.0871   | 12.986    | 1.4583| 14.086   | 1.2891  | 6.434 | .002  |

### Table 3 Comparison of difference of mean IOP of different groups 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      | -2.2629 | .2742 | .605 | -1.714 | .2742 | .016 | -0.5086 | .2742 | .157 |
| T1      | -1.1114 | .2671 | .000 | -2.8371 | .2671 | .000 | -1.7257 | .2671 | .000 |
| T2      | 1.7714  | .3758 | .000 | -5.771 | .3758 | .279 | -2.3486 | .3758 | .000 |
| T3      | .3758  | .3682 | .000 | -7.829 | .3682 | .090 | -2.6514 | .3682 | .000 |
| T4      | .3682  | .3682 | .002 | -5.571 | .3682 | .090 | -1.7600 | .3682 | .000 |
| T5      | 1.4457  | .2858 | .000 | -4.457 | .2858 | .000 | -1.8914 | .2858 | .000 |
| T6      | .6286  | .3077 | .107 | -4.714 | .3077 | .280 | -1.1000 | .3077 | .002 |

### Table 4 Intrigroup Change in Baseline Mean IOP at different time intervals.

| GROUP 1 | GROUP 2 | GROUP 3 |
|---------|---------|---------|
| Mn ch  | SD | %ch | T | P | Mn ch  | SD | %ch | T | P | Mn ch  | SD | %ch | T | P |
| T1      | -1.2714 | .5131 | -9.43 | 14.660 | .000 | -0.4229 | .5951 | -3.07 | 4.204 | .000 | 0.7943 | 1.5197 | 5.576 | -3.092 | .004 |
| T2      | 2.3714  | 1.4942 | 17.60 | -9.389 | .000 | .3371 | 1.4234 | 2.45 | -1.401 | .170 | 2.1771 | .9564 | 15.28 | -13.467 | .000 |
| T3      | 1.9514  | 1.3122 | 14.48 | -8.798 | .000 | .1800 | 1.8453 | 1.31 | .577 | .568 | 1.9629 | 1.5797 | 13.77 | -7.351 | .000 |
| T4      | 1.4829  | 1.3185 | 11.00 | -8.653 | .000 | -0.0171 | 1.6116 | -1.024 | -.063 | .950 | 1.2686 | 1.5901 | 8.906 | -4.842 | .000 |
| T5      | 1.3314  | 1.2204 | 9.88 | -6.455 | .000 | -.3771 | 1.6597 | -2.745 | 1.344 | .188 | 1.0057 | 1.4453 | 7.06 | -4.117 | .000 |
| T6      | 1.1429  | 1.2152 | -1.06 | -6.96 | .000 | -.07486 | 1.5631 | -5.450 | 2.833 | .008 | -0.1571 | 1.8495 | -1.102 | .503 | .618 |
(0.15 mg) was effective in anxiolysis, sedation, stable hemodynamics, and lowering effect on IOP and perioperative endocrine stress responses[11]. The effectiveness of oral clonidine (300 μg) or smaller doses like 22.5 μg/kg as premedication on prevention of IOP rise following IV succinylcholine was confirmed by other studies.[11]

We looked for baseline IOP and IOP post-intubation for 10 minutes in three groups. Group I was administered oral ivabradine, group II was given oral clonidine, while group III was the control group with placebo.

There was a consistent rise in IOP following intubation with iv succinylcholine. However, patient-administered oral clonidine (group II) showed an effective reduction of IOP rise post-intubation with iv succinylcholine compared to subjects on oral ivabradine (group I). The decrease in IOP from the baseline IOP before intubation was consistent at all time intervals in group II subjects. Also, group I had significantly lower IOP as compared to group III only at 1 out of six post-intubation observations. Thus indicating Ivabradine was only marginally better than placebo. However, clonidine was able to attenuate IOP rise effectively.

The range of IOP rise from baseline IOP to IOP following intubation with succinylcholine was very less with clonidine administration in comparison to ivabradine and the placebo group.

Our findings correlated with that of Mahajan et al. I, who also evaluated the effect of clonidine in decreasing the IOP rise and accessed the cardiovascular responses to intubation[12]. They reported that clonidine could effectively decrease IOP rise without any side effects[12].

Boroojeny & Fard (2012)44 c also conducted a randomized, double-blind study to evaluate the efficacy of preoperative oral Clonidine (5 g/kg) in preventing ocular hypertension in the early period after cataract surgery with posterior chamber intraocular lens implantation under general anesthesia[13]. It was concluded that there was no statistically significant difference between the mean IOP 24 hours postoperatively in the two groups[13]. However, compared to preoperative IOP, less mean IOP was seen in the Clonidine group compared to the placebo group[13].

The present study well documented the attenuating effect of clonidine on IOP following intubation. The present study also endorsed its efficacy in controlling the IOP rise following intubation with succinylcholine. However, despite showing a higher reduction in IOP between premedication to reintubation, ivabradine failed to exercise IOP attenuating effect. This could be attributed to the shorter half-life and bioavailability of the drug. Clonidine has almost 3-12 times higher half-life and 1.5 times more bioavailability as compared to Ivabradine.

Conclusion

The result in the present study shows that in comparison to oral Ivabradine, Oral clonidine (0.1 mg) can effectively and safely be recommended as a premedicate for obtunding the rise in IOP following endotracheal intubation after administration of succinylcholine.

Thus it is concluded that oral clonidine is a safe drug for premedication, especially in those patients where the rise in IOP can be dangerous. Nevertheless, still further studies are recommended to corroborate the findings.

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