Comparative Evaluation of The Effect of Oral Clonidine or Oral Diazepam Premedication on Intraocular Pressure Changes Following Suxamethonium and Endotracheal Intubation

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ABSTRACT

Introduction: Rise in intraocular pressure can be deleterious in patients with glaucoma and perforating eye injuries. The aim of this study was to determine if Clonidine used orally as a premedicant could attenuate the rise in IOP that is expected to occur with succinylcholine, laryngoscopy and intubation and we compared it with diazepam.

Material and Methods: Sixty adult ASA I patients receiving general anaesthesia for elective non-ophthalmic surgery were randomly assigned to receive either Clonidine(4-5 mcg/kg) or Diazepam (0.2-0.25mg/kg) ninety min prior to induction of anaesthesia. Propofol was used for induction and succinylcholine for tracheal intubation. IOP, Heart rate and Mean Arterial Pressures were recorded and compared at following intervals: baseline, preinduction, after propofol and succinylcholine and thereafter 1, 3, 5, 7 and 10min following laryngoscopy and intubation.

Results: There was a significant difference in the intraocular pressure when measured about 90min after premedication with the Clonidine group recording lower values. ($p<0.05$). When compared with these baseline values, both groups had a fall in IOP after induction with propofol. Following injection of suxamethonium IOP increased in both groups, but remained below the baseline value in the Clonidine group. Subsequent values showed a declining trend when measured at 1, 3, 5, 7 and 10min after intubation in both the groups but the Clonidine group had lower values at all times. The MAP was also lower in the Clonidine than the diazepam group when measured at the above time intervals.

Conclusion: Oral Clonidine as a premedicant is effective and superior to oral diazepam in attenuating the rise in IOP seen after injection of succinylcholine, laryngoscopy and intubation.

Keywords: Intra-Ocular Pressure, Clonidine, Diazepam, Suxamethonium, Premedicant

INTRODUCTION

Inspite of its undesirable side-effects, suxamethonium continues to be used as the muscle relaxant in patients with difficult intubation and those at risk of aspiration. Succinylcholine causes Intraocular Pressure (IOP) to increase by 6-12mmHg; it lasts for 5-10minutes.[1] Although transient, this can have deleterious effects in patients with glaucoma and perforating eye injuries. Laryngoscopy and intubation can further aggravate the rise in IOP. Methods used to attenuate the effects of suxamethonium on IOP include self-taming, pre-treatment with non-depolarising neuromuscular blocking agents, lidocaine, narcotics, nifedipine, nitroglycerine etc.[1] As Alpha-2-agonists are known to possess IOP lowering effects, we evaluated the efficacy of oral Clonidine in attenuating the rise in IOP that was expected to occur after suxamethonium, laryngoscopy and intubation and compared it with oral diazepam.

MATERIAL AND METHODS

This was a prospective, randomised, double blind, controlled study conducted at TNMC and BYLNair Ch Hospital after approval from the ethics committee and written informed consent from patients. 60 patients aged 18-50 years, ASA I, weighing 40-70kg, either gender, undergoing elective non-opthalmic surgery requiring general anaesthesia, were recruited for the study. Based on a previous study[3] a sample size of 60 would be needed to find a significant difference in IOP with alpha error of 0.05 and 80% power. Patients with anticipated difficult intubation, ocular disease with or without raised IOP, known allergy to any study drug or receiving any medication that could alter the IOP were excluded. During the pre-anaesthetic evaluation, the IOP was recorded in either eye after instillation of topical 4% xylocaine eye drops. The patient was asked to look vertically upward to relax accommodation and the eyelids were separated with the fingers avoiding any pressure on the globe. The Schiotz tonometer (technique accurate to within ±3mmHg) was held by the side arms of the handle, footplate rested on the cornea and the scale reading recorded as soon as the pointer became steady. This was documented as the baseline IOP.

Patients were randomly divided into two groups of 30 each.

Group C: Received oral Clonidine 4-5 mcg/kg, 90minutes prior to surgery

Group D: Received oral Diazepam 0.2-0.25mg/kg, 90 minutes prior to surgery

The tablets used were Clonidine(100 mcg tablet) and Diazepam (5mg tablet) both of which were white in colour, round in shape and of the same size. Three tablets each of either of the two drugs were inserted into similar looking packets. Patients received the premedicants in the following manner based on their weight:

40-49kg: 2 tablets

49.1-59kg: 2.5 tablets

59.1-70kg: 3 tablets

On arrival in the operation room the baseline Heart rate, NIBP, Arterial oxygen saturation (sPO2) and IOP were recorded. This was documented as the pre-induction IOP. The sedation status

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of the patient was graded according to the Ramsay Sedation Scale.[2] After preoxygenation for three minutes anaesthesia was induced with inj fentanyl 2 mcg/kg, inj propofol 2mg/kg followed by suxamethonium 1.5mg/kg. An experienced anaesthesiologist performed the laryngoscopy and intubation after 60 seconds. Patients in whom the tracheal intubation failed at the first attempt were excluded from the study. The haemodymanic variables and IOP were recorded 30 seconds after propofol, 30 seconds after suxamethonium and at 1, 3, 5, 7 and 10mins after intubation. Anaesthesia was maintained with Oxygen +Air+Sevoflurane.

The Heart Rate(HR), Mean Arterial Pressure(MAP) and IOP in both the groups were recorded at the following time intervals and analysed using computer software SPSS 15. IOP was measured in both eyes and the mean of the two was used for statistical analysis.

T0 – Baseline (prior to oral administration of study drug)

Tpre-induction (upon arrival in the operation room approximately 90minutes after the oral administration of the study drug)

Tpropofol- 30seconds after administration of propofol

Tsuxamethonium- 30seconds after administration of suxamethonium

T1- one minute after intubation

T3-three minutes after intubation

T5- five minutes after intubation

T7- seven minutes after intubation

T10- ten minutes after intubation

STATISTICAL ANALYSIS

The parametric data were expressed as Mean ± SD and compared between the two groups using the students t- test. Data within each group were compared with baseline values and analysed using ANOVA and paired t test.

RESULTS

The 2 groups were comparable with respect to age, weight, gender distribution and ASA status.

Intraocular Pressure: There was a significant drop in IOP when recorded on arrival in the operation room as compared to baseline values(before oral administration of study drugs) in the clonidine group whereas it was almost the same as baseline in the diazepam group ($p<.05$) (table-1). Following induction with propofol, there was a significant fall in IOP in both groups; the intergroup comparison of IOP at this interval did not show significant difference. Although the IOP increased after i.v suxamethonium in both the groups the rise was more significant in Group D when both intragroup and intergroup values were compared. The IOP showed a decreasing trend in both groups at 1, 3, 5, 7 and 10min after intubation but Group D recorded significantly higher values than Group C. The magnitude of changes in IOP was also higher in Group D as compared to Group C throughout the study (table-1, 2, 3).

Mean Arterial Pressure: The baseline MAP between the two groups was comparable.MAP was lower when measured 90mins after oral administration in both groups but patients in Group C had significantly lower MAPs than Group D. Both groups recorded significantly lower MAPs after induction with propofol but Group C had lower MAPs as compared to Group D. Following injection suxamethonium and at one minute after intubation, the MAP in Group C increased to more than the pre-

Time	Group Clonidine Intraocular Pressure		Group Clonidine Heart Rate		Group Clonidine Mean Arterial Pressure	
	Mean ±SD	Significance	Mean ±SD	Significance	Mean ±SD	Significance
To	17.57±2.60	S	83±5.50	S	96.88±8.8	S
Tpre-induction	14.19±1.96	S	73.07±5.35	S	89.64±4.6	S
Tpropofol	12.01±0.83	S	72.27±5.19	S	83.89±3.07	S
Tsuxa	15.50±1.82	S	76.53±4.89	S	93.75±5.06	S
T1	17.24±2.44	S	81.90±5.03	NS	95.99±5.7	S
T3	16.20±2.53	S	78.07±4.86	S	88.26±5.6	S
T5	14.83±1.80	S	76.47±4.78	S	86.75±5.7	S
T7	14.31±1.65	S	74.13±4.36	S	84.63±6.06	S
T10	14.11±1.60	S	73.07±3.70	S	84.30±7.2	S
S- Significant, NS- Not significant						

Table-1: Intragroup Comparison of Intraocular Pressure, Mean Arterial Pressure and Heart Rate at different time intervals in the Clonidine Group

Time	Group Diazepam Intraocular Pressure		Group Diazepam Heart Rate		Group Diazepam Mean Arterial Pressure	
	Mean±SD	Significance	Mean±SD	Significance	Mean±SD	Significance
T0	16.60±2.61		81.33±9.22		95.62±5.16	
Tpreinduction	16.00±2.60	S	75.07±8.53	S	88.97±5.52	S
Tpropofol	14.17±1.98	S	73.40±7.69	S	84.78±5.52	S
Tsux	21.03±2.22	S	84.67±6.91	S	99.31±4.10	S
T1	23.12±1.85	S	94.50±5.24	S	105.73±2.87	S
T3	22.00±1.90	S	92.47±5.24	S	103.82±3.69	S
T5	21.12±1.79	S	90.33±5.36	S	101.23±2.81	S
T7	18.49±1.52	S	85.87±5.35	S	98.88±3.71	S
T10	17.43±1.81	S	84.80±5.19	S	97.21±4.79	NS

Table-2: Intragroup Comparison of Intraocular Pressure, Heart Rate and Mean Arterial Pressure at different time intervals in the Diazepam Group

Time	Intraocular Pressure			Heart Rate			Mean arterial Pressure		
	Group Clonidine	Group Diazepam	Significance	Group Clonidine	Group Diazepam	Significance	Group Clonidine	Group Diazepam	Significance
T0	17.57	16.6	NS	83	81.33	NS	96.83	95.62	NS
Tpreinduction	14.1	16	S	73.06	75.06	S	85.56	88.97	S
Tpropofol	12.1	14.1	NS	72.26	73.4	NS	81.66	84.78	NS
Tsux	15.4	21.04	S	76.53	84.66	S	88.47	99.31	S
T1	17.23	23.13	S	81.9	94.5	S	92.24	105.73	S
T3	16.2	22.0	S	78.06	92.46	S	90.64	103.82	S
T5	14.83	21.10	S	76.46	90.33	S	89.52	101.23	S
T7	14.3	18.4	S	74.13	85.86	S	86.64	98.88	S
T10	14.10	17.4	S	73.03	84.8	S	83.53	97.21	S

Table-3: Comparison of IOP, Heart Rate and MAP between Group Clonidine and Group Diazepam

induction level but remained below the baseline MAP while there was significant increase in Group D both in comparison to baseline values and on comparison with Group C ($P<.05$). The MAP showed a decreasing trend at 3, 5, 7 and 10min in both groups with Group C recording significantly lower MAPs than Group D throughout the study period (table-1, 2, 3).

Heart Rate: The groups were comparable with respect to baseline pulse rate. On arrival in the operation room, patients who had received oral Clonidine had a significantly lower heart rate than the diazepam group. There was no significant difference in the pulse rate after propofol both with intragroup and intergroup comparison. While Group D showed a rise in pulse rate after suxamethonium and at 1 min after intubation, Group C showed significantly lower pulse rates ($P<.05$). At subsequent intervals of 3, 5, 7 and 10mins, patients in Group C had lower pulse rates than Group D (table-1, 2, 3).

DISCUSSION

Normal IOP is 10-20mmHg. The factors affecting IOP are movement of aqueous humor, changes in choroidal blood volume, central venous pressure, extraocular muscle tone etc.[4] Many other factors such as genetics, age, refractive error and race are also known to influence the IOP[5] Arterial BP exerts some control over IOP but its effect over a physiologic range of BP is small.[6] Any acute rise in intra-abdominal or intrathoracic pressure, eg during extubation, might increase the IOP. Deep inhaled or intravenous anaesthesia e.g propofol causes a dose related reduction in IOP by 30% to 40%.[7] Opioids have little effect. Ketamine can cause a modest increase in IOP. Alpha-2-agonists provide potentially beneficial effect in ophthalmological surgeries because of their IOP lowering properties.[8] Dexmeditomidine premedication in a dose of 0.6 mcg/kg over 10min blunted the rise in IOP caused by succinylcholine and intubation.[9]

Clonidine has been found to have many beneficial effects when used in the perioperative period as it decreases anaesthetic drug requirements, decreases plasma catecholamine concentrations and hemodynamic stress responses. Clonidine is well absorbed orally and has nearly 100% bioavailability. It is highly lipid soluble and easily penetrates the CNS. The plasma level peaks in approximately 1-2hours and the plasma half life is about 12hours. Premedication with diazepam produces anxiolysis, amnesia and hypnosis. It is also known to blunt the sympathomimetic response associated with laryngoscopy and intubation; probably related to the GABA receptor mediated central inhibitory effects of benzodiazepines.[10] Kumar et al found that oral Clonidine (300 mcg) as premedication could attenuate IOP rises after retrobulbar injection.[11] They also stated that oral diazepam (0.2 mg/kg) had no effect on IOP but iv diazepam (0.15mg/kg) or equivalent doses of midazolam reduced the IOP.

In our study Clonidine premedicated patients had lower IOP values than the diazepam group to begin with. Propofol caused a significant drop in IOP in both groups. Diazepam failed to prevent the rise in IOP following suxamethonium, laryngoscopy and intubation. In the Clonidine group the rise in IOP was less compared with diazepam and although there was an increase above the pre-induction values, it remained below the documented baseline IOP.

It is possible that the prevention of IOP rise with Clonidine was due to attenuation of the haemodynamic response. In the diazepam group a sudden increase in haemodynamic parameters could have overcome the autoregulation of uveal blood flow and resulted in an increase in choroidal blood volume. The reduction in BP does not seem to have a cause effect relationship with the reduction in IOP. Other mechanisms likely to contribute to fall in IOP include reduction in aqueous humor production by direct vasoconstriction of the afferent blood vessels of the ciliary process and inhibition of peripheral cholinergic transmission[12]

Ghignone[13] and Filos[14] found that clonidine in a dose of 5 mcg/kg and 2-2.5 mcg/kg decreased IOP by 35-48% which persisted for 6 hours. Nunes et al concluded that oral Clonidine prevented post-endotracheal intubation induced IOP rises more effectively than lidocaine.[15]

Transient elevation of IOP following cataract extraction is a well recognised complication, sequelae of which can be central retinal artery obstruction and ischaemic optic neuropathy[16], more optic nerve damage in glaucomatous eyes[17], post-operative pain and corneal edema. Boroojeny S et al found that a single dose of oral Clonidine (5 mcg/kg) given 2hours before the cataract surgery prevented acute post-operative IOP rise significantly in the first 12 hours.[18]

Zahedi et al[3] compared the effect of oral Clonidine 3 mcg/kg with oral diazepam 0.15mg/kg two hours before induction of anaesthesia. They concluded that although the Clonidine group had lower IOPs than the diazepam group at all times, the difference between the two groups was significant at 5minutes after succinylcholine injection i.e immediately after tracheal intubation. The MAP and Heart Rate were also significantly lower in the Clonidine group.

In our study, there was a significant drop in the pulse rate

90minutes after oral Clonidine as compared to diazepam. There was no significant change in the heart rate after induction with propofol in either group (p>0.05).Robinson BJ et al studied the mechanism of propofol mediated peripheral vasodilation in humans and concluded that propofol may either reset or inhibit the baroreceptor reflex, reducing the tachycardic response to hypotension.[19] We documented a significantly higher heart rate and Mean Arterial Pressures in the diazepam as compared to the Clonidine group after suxamethonium, laryngoscopy and intubation. Although the Clonidine group also showed increases in haemodynamic parameters after laryngoscopy and intubation, the magnitude of changes was lesser than that observed in the diazepam group. Poutto et al found that noradrenaline levels were lower during and three hours after the surgery in patients premedicated with oral Clonidine.[20] Laurito concluded that oral Clonidine blunts the hemodynamic responses to brief but not prolonged laryngoscopy.[21] On comparing the sedation scores, it was found that in the Clonidine group, 23.3% patients had a Ramsay sedation score of 1 and 76.6% had a score of 2. The diazepam group showed higher sedation scores with 27% having a score of 3 and 73% with a score of 4. None of the patients had a score of 5 or 6.

At the dose of 4- 5 mcg/kg of Clonidine the patients did not experience any hemodynamic instability that needed intervention. However it may be possible to achieve the same attenuation of IOP using a smaller dose of Clonidine thereby avoiding its side-effects.

CONCLUSION

We conclude that oral Clonidine as a premedicant is superior to oral diazepam in attenuating the rise intraocular pressure and mean arterial pressure following suxamethonium, laryngoscopy and intubation.

REFERENCES

1. Chidiac EJ, Ruskin AO, Suxamethonium and the open eye. Opthalmol Clin North Am. 2006;19:279-85.
2. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. BMJ. 1974;2:656-9.
3. Zahedi H, Nekooseresht M, Rahro-Taban M. Medical Journal of the Islamic Republic of Iran. 2007;21:111-114.
4. Murphy DF. Anaesthesia and intraocular pressure. Anesth Analg. 1987;66:135.
5. Joshi C. Bruce DL; Thiopental and succinylcholine action on intraocular pressure, Anaesthesia and Analgesia. 1975;54:471-475.
6. Danlon JV Jr. Anesthesia foe eye, ear, nose and throat surgeries In Miller RD, editor Millers anesthesia. 6th ed Philadelphia Churchill Livingstone; 2005 pg 2531-4
7. Kohli R et al:Int Anesthesiol Clin 45:83;2007.
8. Scheinin B, Lindgren L, Randell T, Scheinin H, Scheinin M. Dexmeditomidine attenuates sympathoadrenal responses to tracheal intubation and reduces the need for thiopentone and peroperative fentanyl. Br J Anaesth. 1992;68:126-31.
9. Mowafi H, Aldossary N, Ismail S, Alqahtani J. Effect of dexmeditomidine premedication on the intraocular pressure changes after succinylcholine and intubation. BrJAnaes 2008.
10. Good Child CS; Gaba receptors and benzodiazepines. British Journal of Anaesthesiology. 1993;71:127-133.
11. Kumar A, Bose S, Bhattacharya A, Tandon OD, Kuncha P. Oral Clonidine premedication for elderly patients undergoing intraocular surgery. Acta Anaesthesiol Scand. 1992;36:159-64.
12. Anthony J, Cunningham. Intraocular Pressure-physiology and implication for anaesthetic management. Anaesthesia Society Journal. 1986;2:195-208.
13. Gignone M, Noe C The effects of Clonidine on IOP, perioperative hemodynamic and anesthetic requirement. Anesthesiol. 1988;68:707-16.
14. Filos KS. A dose response study of orally administered Clonidine as premedication in the elderly; evaluating hemodynamic safety. Anesth Analg. 1993;77:1185-92.
15. Nunez M, Figueira A, Guerra V, Bunos G, Alvarez MI Rodriguez M. Comparative study of Clonidine and lidocaine on the attenuation of the IOP increase associated with laryngoscopy and endotracheal intubation Rev Esp Anestesiol Reanim. 1995;42:312-5.
16. Hayreh SS. Anterior ischaemic optic neuropathy Occurrence after cataract extraction Arch Opthalmol. 1980;98:1410-1414.
17. Savage JA, Thomas JV, Belcher CD, Simmobs RJ. Extracapsular cataract extraction and posterior chamber Intraocular lens implantation in glaucomatous eyes Opthalmology. 1985;92:1506-16.
18. Boroojeny S, Fard M. Journal of Pakistan Medical Association December 2012.
19. Robinson BJ et al. Mechanism whereby propofol mediates peripheral vasodilation in humans.Sympathetic inhibition or direct vascular relaxation? Anaesthesiology. 1997;86:64-72.
20. Poutto J.Schenin B. Oral premedication with Clonidine-effects on stress response during general anaesthesia. Acta Anaesthesiologica Scandinavica. 1987;31:325-329.
21. Laurito CE, Baughman VL Oral Clonidine blunts the hemodynamic responses to brief but not prolonged laryngoscopy. Eur J Clin Anesth. 1993;5:54-7.

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