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Research Article

COMPARISON BETWEEN KETAMINE AND SEVOFLURANE FOR THEIR EFFECT ON INTRAOCULAR PRESSURE IN PATIENTS OF RETINOBLASTOMA DURING EXAMINATION UNDER ANAESTHESIA

Pawni Singh., Sateesh Verma*., Shobhna Jafa., Jyotsna Agrawal., Anita Malik and Asha Awasthi

Department of Anaesthesiology, King George's Medical University, Uttar Pradesh, Lucknow -226003

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A B S T R A C T

Background: Intraocular pressure (IOP) measurement and thorough eye examination are needed for management of retinoblastoma patients. Most children have to be anesthetised for proper eye examination and these anaesthetic agents have tendency to alter IOP. Therefore we aim to compare the effect of ketamine and sevoflurane on IOP in children having retinoblastoma.

Methods: In this prospective study, 100 patients with ASA I/II, for eye examination under anaesthesia were enrolled and randomized into two groups (50 each). Group K was induced byintravenous ketamine 2.0 mg/kg andGroup S byinhalational sevoflurane 8%. IOP was measuredin both eyes at 4 min, 8 min, 12 min and 16 min. The hemodynamic parameters and oxygen saturation were also recorded.

Results: Mean IOP was higher in Group K than Group S at all periods. In Group K the largest increase in IOP from baseline was observed between 8 min to 12 min after that IOP started decline. This decrease in IOP from 12 to 16 min was statistically significant ($p<0.001$). Blood pressure and heart rate were significantly greater in ketamine group at all time periods.

Conclusion: Ketamine had significantly increased the IOP and sevoflurane decreased IOP. Increase in IOP was transient and it does not cross the boundary of clinical significance. Ketamine may be preferred over sevoflurane to avoid falsely low IOP measurement.

INTRODUCTION

Sedation or anaesthesia is usually required in infants and pre-school children if eye examination and intraocular pressure (IOP) measurement has to be done.Retinoblastoma is the most common primary ocular malignancy occurring in children [1].Eye examination in retinoblastoma includes extend of tumour and IOP measurement. Children frequently undergo eye examination to know about response to treatment (i.e. chemotherapy, radiotherapy). Anaesthetic agents may increase or decrease intraocular pressure and their effect may change over time depending on the levels of anaesthesia[2].

Ketamine and sevofluraneare frequently used anaesthetic agent for examination under anaesthesia (EUA). Possible effects of ketamine on intraocular pressure is controversial with some report concluding that it elevates intraocular pressure whereas other suggest that its effects on intraocular pressure is minimal[3,4].Use of ketamine in developed world is declining rapidly.

Corresponding author:* **Sateesh Verma
Department of Anaesthesiology, King George's Medical University, Uttar Pradesh, Lucknow -226003

But in developing countries it is one of the common anaesthetics used because of good safety profile, easy to use and low cost [5]. Ketamine is preferred over sevoflurane in healthcare system which is under-resourced and where new generation anaesthesia machine are not available.

Sevofluraneisfluorinated methyl-isopropyl-ether and it has rapid onset of action, faster recovery time and lower incidence of reported side effects. Sevoflurane is reported to lower intraocular pressure significantly [6, 7].

Only few studies have been done to compare the effects on IOP of sevoflurane and ketamine given by intravenous route[7, 8]. We therefore conducted a randomized prospective study to compare the effect ofketamine and sevoflurane on IOP.The primary outcome measure of the study was IOP in both diseased and non-diseased eye. The secondary outcome measures of the study were heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), SpO_2.

MATERIALS AND METHODS

This prospective study was carried out after getting approval of institutional ethics committee's. The study was carried out in King George's Medical University, Lucknow over the

period of 1 year from September 2014 to September 2015. Children with known case of retinoblastoma posted foreye examination and requiring anaesthesia were included in the study. Hundred out-patients belonging to ASAI or ASAII, scheduled to undergo EUA were recruited for this study. Exclusion criteria were heart disease, hepatic or renal dysfunction, intraocular infection and bilateral retinoblastoma. Routine investigations including blood haemoglobin, total leukocyte count, liver function testand renal function test were carried out as most of our patients were on chemotherapy/radiotherapy. All patients were kept fasting for at least 6 hours prior to anaesthesia. Patients were randomized in to two groups (n=50 in each group) using computer generated random number table.

Intravenous-lines were secured preoperatively. In the operating room monitors were attached and baseline HR, SBP, DBP, MAP and oxygen saturation were recorded. All patients received injection ondansetron 0.1 mg/kg intravenously and injection glycopyrollate 0.004mg/kg intravenously before induction. Anaesthetic agent for induction was given according to group allocated.

Group K: Intravenous ketamine 2 mg/kg body weight and then ventilated with 100% oxygen.

Group S*:* Inhalational sevoflurane 8% with oxygen as carrier gas and maintenance of anaesthesia achieved by sevoflurane at 2 to 4%.

During the induction and maintenance children were ventilated with Jackson-Rees or Bain's circuit. Guedel'soropharyngeal airway was inserted in event of upper airway obstruction. IOP was recorded was at 4min, 8min, 12min and 16 min using a Perkins applanation tonometer. IOP measured at 4 min after starting induction was taken as base line for IOP for subsequent IOP values. IOP was recorded in both diseased and non-diseased eye. The hemodynamic parameters like SBP, DBP, HR and oxygen saturation were recorded before induction of anaesthesia and after induction of anaesthesia (4, 8, 12, 16 minutes).

Propofol and laryngeal mask airway was kept nearby in case its insertion was needed.In postoperative room all patients were nursed in propped up position. Patients were observed for emergence agitation.

All statistical analysis were performed using SPSS 12.0 windows software. The sample size was calculated on the basis of 80% power of the study. Continuous data were summed as Mean±SD (standard deviation) while discrete (categorical) in number and percentage. Continuous groups were compared by independent Student's t test. Categorical groups were compared by chi-square (χ^2) test. A two-tailed p value <0.05 was considered statistically significant.

RESULTS

Data shows that patients of both groups were comparable in regard to age, gender and weight as no significant difference was observed between two groups (Table1).

IOP(diseased eye) in Group K was higher at 8 min (11.9%), 12 min (15.2%) and 16 min (6.6%) as compared to IOP measured at 4 minute. While in Group S, IOP decreased linearly at 8 min (8.5%), 12 min (19.7%) and 16 min (21.4%) as compared to IOP measured at 4 minute. Further, IOP was comparatively higher in Group K than Group S at all time periods.

Table 1 Demographic profile of the patients

Demographic characteristics	Group K (n=50)	Group S (n=50)	p value
Age (month)	37.04 ± 34.12	41.08 ± 32.80	0.548
Sex:			
Female	21 (42.0%)	26 (52.0%)	0.316
Male	29 (58.0%)	24 (48.0%)	
Weight (kg)	12.16 ± 5.50	12.74 ± 5.48	0.598

Data are represented as mean, ±SD, n (%) and ratio. SD=Standard deviation

In non-diseased eye, the IOP show similar trend as of diseased eye except with lower IOP levels in both the groups (Table 2).

Table 2 Intra-ocular pressure (IOP) in both diseased and non-diseased eye (mmHg)

Time (min)	Diseased eye			Non diseased eye		
	Group K (n=50)	Group S (n=50)	p value	Group K (n=50)	Group S (n=50)	p value
4	13.60 ± 3.28	11.80 ± 1.58	0.008*	12.48 ± 3.30	11.16 ± 1.35	0.050*
8	15.44 ± 3.92	10.80 ± 1.76	<0.001**	14.16 ± 3.28	9.88 ± 1.91	<0.001**
12	16.04 ± 3.93	9.48 ± 1.93	<0.001**	14.28 ± 3.43	9.20 ± 1.85	<0.001**
16	14.52 ± 4.00	9.28 ± 1.97	<0.001**	12.76 ± 3.28	9.02 ± 1.62	<0.001**

Data presented as mean ± SD, *=Significant (p<0.01) and**=Significant (p=<0.001)

In Group K, largest increase in IOP from baseline was observed between 8 to 12 minutes after that IOP started to decline towards baseline. This decrease in IOP from 12 to 16 minute was statistically significant (Table3).

Table 3 Comparing p-value of mean IOP changes between the different time periods

Comparison	Diseased eye		Non diseased eye	
	Group K	Group S	Group K	Group S
4 min vs. 8 min	<0.001**	<0.001**	<0.001**	<0.001**
4 min vs. 12 min	<0.001**	<0.001**	<0.001**	<0.001**
4 min vs. 16 min	<0.001**	<0.001**	0.206	<0.001**
8 min vs. 12 min	<0.001**	<0.001**	0.470	0.012*
8 min vs. 16 min	<0.001**	<0.001**	<0.001**	<0.001**
12 min vs. 16 min	<0.001**	0.367	<0.001**	0.417

Data presented as p value, *=Significant (p<0.01) and**=Significant (p=<0.001)

Heart rate (HR) in Group S did not change significantly from baseline whereas in Group K it remained higher than baseline at all time periods (Table 4).

Table 4 Heart rate

Time (min)	Group K (n=50)	Group S (n=50)	p value
Baseline	104.20 ± 16.08	103.64 ± 12.22	0.979
4	109.32 ± 15.03	104.64 ± 12.90	0.104
8	112.86 ± 15.13	103.88 ± 13.45	0.025*
12	114.10 ± 15.36	102.86 ± 13.54	0.004*
16	112.20 ± 16.15	102.82 ± 12.18	0.027*

Data presented as mean ± SD, *=Significant (p<0.01)

Increase in MAP was observed in Group K while it was decreased in Group S. Furthermore the MAP remained higher in Group K than Group S at all post periods (Table-5). Statistically on comparing the MAP at different time, between the groups test showed significant (p<0.001) difference (Table 5).

Table 5 Mean arterial pressure (MAP)

Time (min)	Group K (n=50)	Group S (n=50)	p value
Baseline	69.88 ± 8.63	70.83 ± 7.32	0.868
4	73.37 ± 8.19	70.14 ± 7.52	0.194
8	74.89 ± 9.10	67.75 ± 9.10	0.003*

12	76.62 ± 9.40	66.50 ± 11.30	0.001**
16	74.62 ± 9.45	65.44 ± 12.17	0.001**

Data presented as mean ± SD, *=Significant (p<0.01) and**=Significant (p=<0.001)

SBP, DBP, MAP, HR were significantly greater in ketamine group at all intervals. In ketamine group there was increase in BP and HR up to 12 min and thereafter it started to decline. It followed the same pattern as that of IOP and all the changes in haemodynamic started coming back to baseline after 12 minutes. In sevoflurane group, SBP, DBP and MAP declined significantly from 8min to 12min interval and thereafter it became stable.

SpO_2 values were similar in both groups and no significant difference was found.

In Group K, one patient (2.0%) needed LMA insertion and 47 patients (94.0%) had no complications. In Group S, 2 patient (4.0%) had agitation on emergence, and 2patient (4.0%) needed LMA insertion and 44 (88.0%) had no known complications.

DISCUSSION

In our study, we found a statistically significant increase in IOP in children anaesthetised with ketamine. The trend of riseof IOPin comparison to first reading was 11.9%, 15.2% and 6.6% higherat 8 minutes, 12 minutes and 16 minutes in diseased eye. Similar increase in IOP baseline was observed in non-diseased eye. In ketamine group largest increase in IOP from baseline was observed from 8 to 12 minutes after drug administration thereafter it started to decline towards baseline at 16 min. As the haemodynamic effect of ketamine coincide with this time period, it is very unlikely that IOP would increase after this time period. IOP measured at 4 min after starting induction (baseline IOP) was higher in ketamine group as compared to sevoflurane group. This difference in IOP was noticed because inducing agents had already influenced the IOP before first IOP measurement could be taken. Although increase in IOP at 8, 12 and 16 min interval was statistically significant, but no clinical harmful IOP levels (>24mmHg) was found in our study [9, 10].

Our findings agree with study conducted Jones *et al*.(2010) on Intra-ocular pressures in children with glaucoma undergoing examination under anaesthesia [7]. Patients were induced with ketamine and anaesthesia was maintained with sevoflurane. IOPs were measured after ketamine and then rechecked after sevoflurane. They concluded that sevoflurane lowers the IOP significantly compared with the IOP measured after ketamine. They stated that ketamine was a better inducing agent when accurate IOP measurement was required.

Blumberg *et al*. (2007) conducted a study to know effects of sevoflurane and intramuscular ketamine on IOP in children during examination under anaesthesia [8]. They reported that IOP in the ketamine group was higherthan sevoflurane. In the ketamine group HR, SBP and DBP were significantly higher than sevoflurane. They concluded that IOP measured after ketamine sedation is more likely to represent the awake IOP and its value would be more accurate.

Our findings agree with a recently published study by ShernazWadia *et al*.(2014) on Ketamine and Intraocular Pressure in Children, which concluded that ketamine causes increase in intraocular pressure that at times transiently exceeded the bounds for potential clinical importance (5 mm Hg) [11]. Similarly in our study 2 out of 50 patients had an increase of IOP up to 24 mmHg. However this increase in IOP was transient as the highest recorded IOP was at 12 min and after that it started to decrease.

Previous study reported that the three was not clinically meaningful associations of ketamine (≤4 mg/kg) with elevation of IOP dosages [12]. Patients in this study were children without ocular abnormalities undergoing miner procedures. This study differs from ours as we included children with eye disease and our result shows that IOP increase due to ketamine was statistically significant although it was not clinically significant. Difference in result may be because of most of their subjects received midazolam, which may have blunted this effect.

Altiparmak B *et al*. (2015) reported the effects of ketamine pre medication in 100 children with retinoblastoma undergoing ophthalmic surgery and showed that oral ketamine was a safe and effective way of premedication for oncologic patients undergoing EUA, adverse effects were seen rarely while IOP remained normal in most of the patients [13].

Another study (Park J *et al*., 2013) compared the effects of desflurane with sevoflurane and found that sevoflurane significantly lowered IOP [6]. Drop in IOP in this study was similar to our study but patient population was different i.e. higher age group and different eye disease.

A previous study (Nagdeve NG *et al*.,2006) reported the effect of different doses of ketamine on intraocular pressure [14]. In this study children were induced and maintained with halothane, and ketamine was given 10 minutes after induction. They concluded that ketamine has a dose-dependent effect on IOP, with 6 mg/kg it causes a small increase in IOP and with 3 mg/kg there was no change in IOP. The higher dose of ketamine also was associated with an increased incidence of postoperative complications. Similar to this study we found that SBP, DBP, MAP, HR were significantly greater in ketamine group at all intervals.

Limitation

In our study IOP was measured by multiple healthcare providers thus it has chances of interpersonal variability. We could not measure IOP before the induction of anaesthesia due to lack of cooperation in children. IOP measured at 4 min after starting induction was taken as a base line for subsequent IOP values. Glycopyrrolate was used in our study which could be act as confounding factor.Further small sample size may have underpowered our result. For future we recommend that effect of ketamine on IOP could be studied at different doses of ketamine on bigger sample size.

CONCLUSION

Ketamine increases in IOPwhile sevoflurane lowers the IOP significantly. But increase in IOP due to ketaminewas transient and it lasted only for few minute. Thus ketamine may have advantage over sevoflurane in children for IOP measurement and eye examination as it is safer to have a falsely high IOP than a falsely lower IOP as the latter may result in treatment being delayed.

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Staffmembers of department of anaesthesiology

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