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RESEARCH ARTICLE
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EFFECTS OF LOW DOSES OF KETAMINE ON INTRACRANIAL PRESSURE IN PATIENTS HAVING SPACE OCCUPYING LESION OF THE BRAIN

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Abstract

Background

Expansion of intracranial contents by a space-occupying lesion (SOL) leads to compression and distortion of the tissues of the CNS and can increase intracranial pressure(ICP). It was presumed that ketamine can cause a dangerous increase in ICP by increasing blood pressure. The present study was conducted to investigate the effects of low doses of ketamine on ICP in patients having space occupying lesion of the brain.

Methods

The study was conducted on 45 patients after obtaining approval from ethical committee. Patients included were posted for elective supratentorial surgeries for brain tumour excision. Standard induction was done intravenously in all patients with propofol, fentanyl and vecuronium with 5ml of normal saline (Group A), 0.25mg/kg ketamine diluted to 5ml (Group B), 0.5mg/kg ketamine diluted to 5ml (Group C). Optic nerve sheath diameter(ONSD) measurement by ocular sonography which serves as an indirect non-invasive technique to measure ICP was recorded at 3 instances i.e. before start of IV boluses of drugs, at 2 mins of bag and mask ventilation and at 5 mins of post endotracheal intubation.

Result

ONSD values were comparable in all three groups at baseline. ONSD value decreased in all groups after 2 minutes of BMV and were comparable in all groups. Values slightly increased at 5 minutes after endotracheal intubation as compared to 2 minutes; though values were lesser than baseline in every group.

Conclusion
Our study refutes the old opinion that ketamine increases ICP. Combined with a benzodiazepine and barbiturates, ketamine may be the preferred sedative/anaesthetic agent for patients with space occupying lesion and can reduce ICP as well.

Keywords: Ketamine, Optic nerve sheath diameter, Intracranial pressure, Supratentorial tumour, Neuroanaesthesia

INTRODUCTION

The brain and spinal cord are enclosed by bone. Intracranial pressure (ICP) is defined as the pressure within the cranium which comprises a fixed volume of neural tissue, blood and cerebrospinal fluid (CSF). Normal ICP varies according to age and ranges between 5 mmHg and 15 mmHg in adults [1]. Expansion of intracranial contents by a space-occupying lesion (SOL) leads to compression and distortion of the tissues of the CNS. Slowly enlarging SOLs can be accommodated by atrophy of adjacent brain or spinal tissue. [2] In patients with intracranial space-occupying lesions, control of mean arterial (MAP) and intracranial (ICP) pressure during anaesthetic induction and tracheal intubation is essential to prevent an untoward increase or decrease in cerebral perfusion pressure (CPP).
Bedside sonographic measurement of optic nerve sheath diameter(ONSD) is emerging as a non-invasive technique to detect elevated ICP. Increased ICP is transmitted to the subarachnoid space surrounding the optic nerve, causing optic nerve sheath expansion, and the expansion of this cerebrospinal fluid (CSF) space can easily be detected using ultrasound.[4] Because ultrasound techniques are abundantly used in operation theatres at present and are readily available, they can be used to measure the ONSD for the early diagnosis in patients at a high risk for increased ICP. [5]

In patients with various intracranial pathologies and reduced intracranial compliance, adequate sedation and analgesia is the basic important measure to control ICP along with controlled ventilation. Deepening sedation is one of the routine first steps when ICP rises. The commonly available sedative and hypnotic agents are benzodiazepines, propofol, and barbiturates. These agents are known to decrease blood pressure and may potentially decrease CPP. [6]

Ketamine was first introduced as a dissociative anesthetic for use in neurological surgery in 1970 since it would not suppress respiratory function and had an overall sympathomimetic effect on the cardiovascular system [7]. It quickly fell out of favor in neurosurgical patients because initial research stated that ketamine can cause a dangerous increase in ICP and thus a decrease in cerebral perfusion and oxygenation [8]. However more recent research has shown that ketamine may be efficacious for patients with TBIs and can decrease ICP [9].
Due to the conflicting literature, the present case control observational study was conducted to investigate the effects of low doses of ketamine on intracranial pressure in patients having space occupying lesion of the brain.

MATERIAL AND METHODS

The present hospital based, observational, experimental study was conducted in the department of Neuro-anaesthesiology at Mahatma Gandhi Medical College and Hospital, Jaipur. This study was conducted over a time span of one year (October 2022 to October 2023). The study was performed after obtaining ethical committee approval and written informed consent from all participants before enrolment into the study. The patients were selected according to the following inclusion criteria- patients with ASA class I/ II, aged 18-55 years, scheduled for elective supratentorial brain tumour excision surgery, tumour size more than 2.5 cm having symptomatic and radiological evidence of raised ICP . Exclusion criteria were patients with ASA class III, IV & V, patients having predicted difficult airway and refusal to give consent.

After applying the inclusion and exclusion criteria, 45 patients were selected for the present study. In operation theatre standard American Society of Anaesthesiologists (ASA) monitoring was done for all the patients. Selected patients were divided into 3 groups i.e. Group A, Group B and Group C. Selection of the drug under study was done by double blinding and randomization by chit method. the person who was not involved in the anaesthesiologist's team for that particular patient. **Group A** was induced with standard induction agents 1-2 μg/ kg of fentanyl, 0.1 mg / Kg vecuronium, 2-3 mg/kg of propofol and 5 ml of normal saline (placebo) through intravenous (IV) route. **Group B** was induced with 1-2 μg/ kg of fentanyl, 0.1 mg / Kg vecuronium 2-3 mg/kg of propofol and 0.25 mg/kg of ketamine diluted with normal saline in 5ml volume. **Group C** was induced with 1-2 μg/ kg of fentanyl, 0.1 mg / Kg vecuronium 2-3 mg/kg of propofol and 0.5 mg/kg of ketamine diluted with normal saline in 5ml volume.
Patients were pre-oxygenated with 100% O_2 for 3 minutes. After administration of intravenous (IV) drugs all patients were intubated with appropriate size endotracheal tube, 1% propofol infusion @ 50-200 mcg/kg/hr was started just after intubation and patients were ventilated with 50% O_2, 50% air.

Ocular ultrasonography (USG) were performed on a Sonosite Micromaxx machine with a 10–5 MHz linear probe using a standard technique i.e. 3mm behind the eye globe using B-mode. Briefly, subjects were examined in the supine position. Conductive US gel was placed over a closed eyelid. A linear probe was used to obtain axial cross-sectional images of the optic nerve, and the ONSD was measured 3 mm posterior to the orbit. Readings were taken at 3 different intervals i.e. before start of IV boluses of drugs, at 2 mins of bag and mask ventilation and at 5 mins of post endotracheal intubation. (Figure 1)

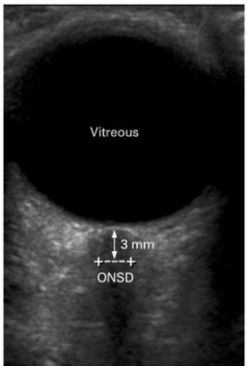

Figure 1

At the end of surgery patients were reversed using a combination of injection neostigmine 0.05 mg/kg iv and injection glycopyrrolate 0.01 mg/kg iv and extubated after achieving adequate respiratory efforts. After extubation, patients were shifted to Post Anaesthesia Care Unit for post-operative monitoring.

ICP MEASUREMENT BY ONSD

There is lot of disparity in available literature for the upper cut-off value of ONSD but many has identified it near about 5 mm, above which patients exhibit either clinical or radiologic signs of elevated ICP.[10**]** Hence in the present study, same standard was used. ONSD cut-off values of 4.7 mm was used(as mentioned in the literature the cut-off 4.6 mm for females and 4.8 mm for males were used for the diagnosis of elevated ICP).[11]

STATISITCAL ANALYSIS

Data so collected was tabulated in an excel sheet, under the guidance of statistician. Data was analyzed using IBM SPSS. Statistics Windows, Version 24.0. (Armonk, NY: IBM Corp) for the generation of descriptive and inferential statistics. The statistical significant difference among groups was determined by the anova test.

Table 1: Demographic characteristics of the study population.

Variables	Group A (n=15)	Group B (n=15)	Group C (n=15)
Male n (%)	10 (66.67)	12 (80)	9 (60)
Female n (%)	5 (33.33)	3 (20)	6 (40)
Age (Mean±SD)	43.2±7.19	41.3±6.79	44.68±8.12

Table 2: Mean arterial pressure (MAP), heart rate (HR) at baseline, after 2 minutes of induction and 5 minutes after tracheal intubation.

Baseline	Group A, (N=15)		Group B, (N=15)		Group C, (N=15)		p value
	Mean	SD	Mean	SD	Mean	SD	
MAP (mmHg)	92	4	93	4	93	4	0.81
HR (bpm)	86	6	86	7	85	6	0.92
After 2 Min of BMV							
MAP (mmHg)	91	3	90	3	89	4	0.71
HR (bpm)	89	5	93	7	92	4	0.24
After 5 Min of Intubation							
MAP (mmHg)	93	4	91	3	94	6	0.58
HR (bpm)	89	5	93	7	92	4	0.24

Table 3: Optic nerve sheath diameter (ONSD) values at baseline, after 2 minutes of induction and 5 minutes after tracheal intubation.

	Group A (Mean ± SD)	Group B (Mean ± SD)	Group C (Mean ± SD)	P value
Baseline	**5.4±1.67**	**5.4±1.56**	**5.3±1.76**	**0.81**
Post 2 mins of BMV	**4.8±1.4**	**4.8±1.03**	**4.9±0.98**	**0.83**
Post 5 min of intubation	**4.94±1.1**	**5.1±0.82**	**5.0±0.93**	**0.42**
P- value	**0.29**	**0.22**	**0.44**	

RESULTS

Demographic profiles in all the three groups were comparable as shown in table 1.Table 2 shows the mean arterial pressure (MAP) and heart rate (HR) at baseline, 2 minutes after BMV and 5 minutes after tracheal intubation. Statistically no significant difference was found among the three groups. There was little increase in HR (bpm) among the three groups after post-tracheal intubation at two and five minutes which was statistically not significant (table 2).

In the present study as shown in table 3, OSND values varies from 4 to 5.8 mm among all the groups at baseline, with mean of 5.4mm, 5.4mm and 5.3mm among group A, B and C respectively. In group A, B and C, post BMV at 2 minutes, mean OSND values decreased to 4.8mm, 4.8mm, 4.9mm respectively and at 5 minutes after tracheal intubation values were 4.94mm, 5.1mm, 5mm respectively. At 5 minutes after tracheal intubation, ONSD values increased slightly as compared to 2 minutes but in all groups values were lower than baseline indicating decrease in ICP in all groups.

DISCUSSION

Ketamine is a short-acting, fast-onset dissociative drug that induces effective sedation, and analgesia with a high safety margin. In its effective therapeutic range, it does not depress spontaneous ventilation and does not lower blood pressure. As such, ketamine would be an optimal drug for short interventions in emergency situations and in unstable patients.

The notion that ketamine increases ICP stems from several case reports and case series published mostly between 1970 and 1972, shortly after ketamine was introduced as an anesthetic agent in the mid-1960s [12-18]. Increases in ICP were observed following administration of ≥ 2-mg/kg doses of ketamine for short diagnostic or surgical procedures in awake children and adults**.** Almost all of these ICP elevations were observed in patients with an obstructed ventricular system, mostly due to malfunctioning ventriculoperitoneal shunts or in those with no shunts at all. These elevations were observed in patients who were breathing spontaneously, although most of the reports stress that the

patients continued to breath effectively and that their arterial or end-tidal PCO2 did not increase .[19] The ICP increased only in patients who had received ketamine as a sole anesthetic agent or who were only lightly anesthetized with nitrous oxide**.** The ICP did not increase when thiopental was administered before ketamine, and when thiopental was administered following ketamine-induced ICP elevation, ICP decreased promptly**.** [20]

In the present experimental study, we studied the effects of ketamine on ICP in patients with space occupying lesion of the brain, in light of the long-standing, deeply entrenched opinion that ketamine increases ICP. Based on preliminary observations, we hypothesized that ketamine will not only, not increase ICP but that it may effectively reduce it and prevent potentially detrimental ICP elevations during distressing interventions in susceptible patients. Our results clearly show that in well sedated, mechanically ventilated patients having brain SOL, ketamine in the used dosages decreases ICP rather than increasing it. Similar results were seen by a retrospective observational study by Dengler et al which stated that ketamine boluses are associated with a reduction in ICP [9]. Two studies conducted by Bourgoin et al. and Cohen et al. had similar conclusions and both articles stated that ketamine does not produce adverse patient outcomes regarding ICP and CPP in patients with acute TBIs [21,22]. Another study conducted in patients with severe TBI who were sedated with propofol, Albanèse et al found that ICP decreased following ketamine administration. [23]

In our study, ONSD values decreased after 2 minutes of BMV due to hyperventilation and administering adequate analgesia and sedation. Values increased slightly after 5 minutes of intubation probably due to stimulation caused by endotracheal intubation. Also notable is that ONSD values decreased after giving ketamine rather increasing, opposing the old opinion that it increases ICP.

From the results of the present study, it can be said that although our findings were observed in sedated, mechanically ventilated patients, we believe that they may be applicable to other patient populations and clinical scenarios.

CONCLUSION

In patients with space occupying lesion undergoing mechanical ventilation, ketamine effectively decreased ICP and prevented untoward ICP elevations during potentially distressing interventions, without lowering blood pressure. These results refute the notion that ketamine increases ICP. Combined with a benzodiazepine and barbiturates ketamine may be the preferred sedative/anaesthetic agent for patients with space occupying lesion, and it can probably be used safely in surgical situations.

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