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COMPARISON OF KETOFOL AND PROPOFOL IN INTRACRANIAL ANEURYSMAL CLIPPING SURGERY: A PROSPECTIVE RANDOMIZED CONTROL STUDY

Anesthesiology

Dr Ajit Bhardwaj M.D Anaesthesia, DM Neuroanaesthesia Asst. Prof. Anaesthesiology, Command Hospital, Lucknow

Dr Arpit Garg* M.D.Anaesthesia Asst. Prof. Anaesthesiology, Command Hospital, Lucknow *Corresponding Author

Dr Priyanka Arora Asst Prof Ophthalmology.

ABSTRACT

Background: Haemodynamic stability is the major goal of anaesthesia during intracranial aneurysm clipping . In the present study, we compared the effects of ketofol with propofol alone, used as an induction and maintenance agent during surgical clipping of intracranial aneurysm.

Material and methods - Forty patients aged 18 to 75 years, posted for aneurysm neck clipping following aneurysmal Subarachnoid haemorrhage (SAH) were included in the study. The patients were randomized into two groups. One group received combination of ketamine and propofol (1:5 ratio) (Group KP) and the other propofol (Group P) for induction and maintenance of anaesthesia.

Results - Combination of Ketamine and propofol (in the ratio of 1:5) which was used in this study provided for better maintenance of Mean Arterial Pressure(MAP) during induction and maintenance of anaesthesia.

Conclusion – Ketofol compared to propofol alone provides better hemodynamic stability on induction as well as during maintenance of anaesthesia in intracranial aneurysmal clipping surgery without increasing intracranial pressure.

KEYWORDS

Ketofol, aneurysmal clipping, hemodynamic stability , intracranial pressure, brain relaxation.

INTRODUCTION

In aneurysm clipping surgery, goals of anaesthesia include maintenance of adequate cerebral perfusion pressure, cerebral oxygenation, hemodynamic stability and brain relaxation to facilitate neurosurgical procedures and avoidance of technique or agents that affects these factors.[1]

Propofol mechanism of providing general anesthesia is by facilitation of inhibitory neurotransmission mediated by GABA.[2,3] Its main advantages are its rapid induction and recovery, anticonvulsant and antiemetic effects, reduction of Cerebral blood flow (CBF) and Intracranial pressure (ICP). Its main disadvantage lies in its dose dependent fall in BP and respiratory depression.[4-6] Ketamine is an NMDA receptor antagonist and its mode of action is by inducing anesthesia through thalamo-cortical dissociation.[7]Several advantages have been attributed to ketamine starting from its analgesic effect at subanaesthetic doses, maintenance of muscle tone, protecting airway reflexes, spontaneous respiration and maintenance of greater Cerebral perfusion pressure (CPP) . It was also presumed that ketamine increases intracranial pressure.[8,9]During sedation and controlled ventilation, ketamine does not increase CBF and ICP but maintains a greater CPP due to its sympathomimetic effects[10]. It was anticipated that combining both drugs will result in a mixture which has additive effects so that the dose of individual drug can be reduced and benefit of both the drugs such as, analgesia, hypnosis amnesia and hemodynamic stability can be achieved.

The primary goal during induction of anaesthesia for aneurysmal clipping is to prevent any changes in Transmural Pressure (TMP= MAP – ICP) which may precipitate aneurysm rupture. Maintenance of Arterial blood pressure (ABP) is very important during induction of anaesthesia. Any significant decrease in MAP because of vasodilation by anaesthetics (like propofol) may lead to cerebral ischemia. Also reflex vasodilation of cerebral blood vessels may cause brain swelling and increased ICP which may further aggravate cerebral ischemia. Therefore a balance should be made between maintaining CPP and minimizing TMP.[11]

Ketofol is a stable mixture (made by combining ketamine and propofol) and has been used effectively in operation theater as well as in ambulatory settings. [3,5,9] Several studies have been carried out and role of ketamine with regards to intracranial pressure has been reevaluated.[12-14] Some studies showed that during ketamine use, ICP depends on several variables like controlled ventilation, other anesthetic agents, and use of other drugs.[15,16]In patients with severe head injury, Ketamine use has been found to be safe under controlled settings.[17-19]Samar et al studied[20] effects of ketofol for sedation in awake craniotomy procedures, it was seen that mean ICP (as measured by burrhole procedure) significantly decreased prior to dural opening compared to both baseline values. Ketamine when used for sedation as well as inducing agent for rapid sequence induction in traumatic brain injury patients did not increase ICP. [21,22]

MATERIAL AND METHODS

This study enrolled forty patients aged 18 to 75 years (after ethical committee approval), posted for aneurysm neck clipping following aneurysmal SAH . Patients who were conscious and in World Federation of Neurological Surgeons(WFNS), Hunt and Hess and Fischer grade 1 or 2 after SAH were recruited into this study. Patients who were unconscious or had raised ICP (Optic Nerve Sheath Diameter >5.5 mm which correlates with ICP >15 mm of Hg) were excluded. Also patients with coronary artery disease, giant aneurysm, psychiatric disease or any other neurological or neurodegenerative disorders were excluded from the study . Group P comprised of patients who received Propofol for induction and maintenance of anaesthesia and group KP received combination of Ketamine and Propofol (1:5) for induction and maintenance of anaesthesia The surgery was performed by an experienced neurosurgeon who also provided for intraventricular ICP measurement and evaluated the brain relaxation according to the scoring system.

Study drug preparation:

In a 50ml syringe- 48 ml study drug was loaded.

Group P: 48 ml of Propofol 1% (10mg/ml). [1mlof study drug contains Propofol 10mg].

Group KP: 40 ml of Propofol 1% (10mg/ml) + 8 ml of Ketamine (10mg/ml). [1 ml of study drug contains 8.33 mg of Propofol + 1.67 mg of Ketamine].

Study drug infusion:

For Induction of Anaesthesia: Study drug was infused at a rate of 2.4 ml/kg/hr and was decreased to 0.3ml/kg/hr at the loss of verbal response.

For Maintenance of Anaesthesia: Study drug was infused at a rate of 0.3 ml/kg/hr titrated to maintain hemodynamic stability. Study drug infusion rate was titrated (0.3-0.6ml/kg/hr)according to MAP to keep MAP within 20% of the base line value.

Fentanyl was administered intravenously in dose of 2µg/kg prior to induction of anaesthesia followed by 1- 2 µg/kg/hr as infusion for intraoperative analgesia. Induction of anaesthesia was achieved by infusion of the study drug and infusion was reduced to maintenance dose at the loss of verbal response of the patient. After induction of

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anaesthesia, bolus dose of intravenous vecuronium 0.1 mg/kg was given for endotracheal intubation under NMT monitoring. Lignocaine 1.5mg/kg was given 90 seconds prior to laryngoscopy to attenuate the intubation response. Patients were intubated when TOF count was zero. They were ventilated with volume controlled ventilation with tidal volume of 8ml/kg body weight with 50% oxygen in air to maintain an ETCO2 of 35-40mm of Hg. Study drug infusion was decreased to 75% of the original infusion rate at the beginning of closure of duramater, reduced to 50% of the original rate at the beginning of muscle closure and further decreased to 25% of the original infusion rate at the beginning of skin closure. Study drug infusion was stopped at the end of skin suture. Fentanyl infusion was stopped after dural closure.

Outcome measures and definitions

Hemodynamic parameters HR, MAP, SPO_2 and $ETCO_2$ were recorded at different time periods from the beginning of anaesthesia to postoperative period of 12 hrs. Study drug infusion rate was titrated according to MAP to keep blood pressures within 20% of the base line value.

Intraventricular ICP Mesurement

Intraventricular ICP was measured by the operating surgeon using burr hole craniotomy without any loss of CSF, through pressure transducer system. The recording was noted at one minute intervals for three minutes. The maximum of three values was considered as the intraventricular intracranial pressure of the patient.

Assessment of brain relaxation

Brain relaxation was assessed on a grading system given by Madhusudhana etal[23] A blinded operating neurosurgeon (> 5 yrs experience) assesed brain relaxation score before opening of duramater as described below.

Grade 4: The brain surface is jutting out or expanding beyond the craniotomy margin and brain pulsation not clearly defined.

Grade 3: Brain surface will be at the level of craniotomy margins and brain pulsations observed faintly.

Grade 2: Brain surface lies just below the surface of craniotomy region margin and brain pulsations well seen.

Grade 1: Brain surface below the surface of craniotomy margin and well retracted into the cranial cavity with good brain pulsations.

RESULTS

Patient characterstics

The demographic and patient clinical profile was comparable in both the study groups.

TABLE 1- Patient characterstics

PARAMETERS	KETOFOL(KP) (n=20)	PROPOFOL(P) (n=20)	P value
Age (yr)	48.35+12.419	50.15 + 8.689	0.598
Sex (M/F)	14/6	11/9	0.327
WEIGHT	64.55 + 8.556	59.65 + 8.45	0.076
HUNT & HESS	17/3	17/3	1.000
WFNS (1/2)	16/4	16/4	1.000
FISHER (1/2)	1/19	1/19	0.311
ONSD (mm)	4.79 + 1.483	4.73 + 1.418	0.199
SURGERYTIME (min)	158.4 + 24.648	152 + 16.255	0.338
ANES TIME (min)	184.3 + 40.566	182.75 + 15.515	0.774
HB BASELINE (gms)	13.065 +1.346	13.325 + 1.646	0.588
Crystalloids (ml)	2282.5 +246.128	2197.5 + 271.679	0.306
Urine Output (ml)	865 + 202.029	854 + 123.391	0.836

The values were expressed as mean ± SD and were analysed using independent t test
* p value < 0.05 was considered significant

Clinical and anaesthetic characterstics:

Intraventricular ICP

Mean ICP in Ketofol group was 11.64 mm of Hg and in propofol group was 11.47 mm of Hg. (p=0.802). ICP values ranged from 8.7 to 16 mm of Hg in KP group and from 8.7 to 15 mm of Hg in P group.

Brain relaxation- Brain relaxation in both the study groups were comparable. Median was grade 3 in both the groups (p=0.977).

2. INTRAOPERATIVE PARAMETERS

Mean Arterial Pressure

Mean arterial pressure was measured in both the groups at different stages to know the effect of anaesthetic agents used as maintenance agents. The pre-induction MAP was comparable in both groups (p=0.101) but there was a significant difference in MAP on induction (p=0.038) and maintenance of anaesthesia (p=0.0001). This shows that MAP was significantly low on induction as well as during intraoperative period in-group P as compared to group KP .

Table 2 - Mean Arterial Pressure

MEASUREMENT POINT	Group KP n=20	Group P n=20	p- value
Preinduction	100.1 ± 6.593	103.25 ± 5.169	0.101
Induction	97.0 ± 8.651	83.5 ± 4.658	**0.038***
Head pin application	103.85 ± 6.18	102.55 ± 6.67	0.883
Burr hole	98.20 ± 7.08	68.90 ± 4.17	**0.0001***
Starting Craniotomy	96.15 ± 6.32	68.00 ± 4.63	**0.0001***
Bone flap removal	98.90 ± 6.11	61.95 ± 4.95	**0.0001***
Dural opening	93.70 ± 4.97	71.70 ± 5.29	**0.0001***
Temporary clipping	96.90 ± 3.91	73.85 ± 7.65	**0.0001***
Permanent clipping	90.75 ± 6.30	70.10 ± 4.52	**0.0001***
Dural closure	98.65 ± 7.08	75.20 ± 7.89	**0.0001***
Muscle suture	102.6 ± 6.40	78.05 ± 6.44	**0.0001***
Skin suture	103.55 ± 6.31	101.25 ± 6.81	**0.0001***

The values were expressed as mean ± SD and were analysed using independent t test
* p value < 0.05 was considered significant

Heart Rate and $ETCO_2$ were comparable in both study groups with no statistically significant difference.

Table 3 Anaesthesia drugs

DRUGS	KP (N=20)	P (N=20)	P VALUE
Fentanyl(micrograms)	278.5	285.15	0.695
Propofol(mg)	778	871.5	0.035*
Vecuronium(mg)	14.65	14.50	0. 796
Ketamine(mg)	162.55	0	

The values denote mean value of anaesthesia drugs used per patient in both the groups. Values are expressed as mean and were analysed using independent t test.
* p value < 0.05 was considered significant

Table 4-Rescue drugs used

	KP (N=20)	P (N=20)	p VALUE
SBP >20% fall(No. of patients)	3 (15%)	9 (45%)	**0.002***
Phenylephrine required (No. of patients)	2 (10%)	7 (35%)	**0.020***
SBP >20% rise (No. of patients)	5 (25%)	3 (15%)	0.693
Esmolol required (No. of patients)	4 (20%)	3 (15%)	1.000

The values were expressed as no. of patients (%)
* - p value< 0.05 was considered significant.

DISCUSSION

Intracranial pressure

In this study, mean intraventricular ICP in group KP was 11.64 mm of Hg and in group P it was 11.47 mm of Hg (p=0.802). Mean ICP values in both the groups were in normal range. This suggests that ketamine when mixed with propofol in ratio of 1:5 did not increase ICP in patients undergoing intracranial aneurysm clipping surgery.

Several studies from the 1970s[13,24-26] had showed an association between ketamine and increased ICP in patients who had an intracranial pathology like obstructive hydrocephalus, aqueductal stenosis and intracranial lesions causing mass effects. When healthy patients on mechanical ventilation were given ketamine for sedation it was found that there was no statistically significant increase in ICP.[26]

Brain relaxation

Brain relaxation is an important aspect of anaesthetic care during

intracranial surgery. Optimal brain relaxation improves the surgeon's operating conditions and is likely to minimize the severity of retraction injury, [27-31] with the potential for providing the patient with a better outcome.

This study found the same quality of brain relaxation in both the study groups. (p>0.05). Several studies have shown that in comparison to inhalational anaesthetics, i.v. anesthetics reduce ICP [32-34]; but, various anaesthetic techniques have not shown any difference in brain relaxation.[35]

Hemodynamic stability

There was greater then twenty percent fall in MAP in 45% of patients receiving propofol alone as compared to only 15% of patients receiving combination of ketamine and propofol during induction of anaesthesia (p =0.038). Also, ketofol provided better hemodynamics during maintenance of anaesthesia. There was statistically significant difference in the use of rescue drugs used as depicted in Table 4. We ascribe this to sympathomimetic action of ketamine because of which there was not as much fall in MAP with ketofol. Earlier studies with ketofol[36-38] have shown that MAP is better maintained with ketofol as compared to other intravenous anaesthetic agents. This study used a low dose ketamine-propofol mixture in the ratio of 1:5 anticipating that it would be just enough to prevent fall in MAP induced by vasodilation due to propofol and also not cause too much sympathomimetic effect so as to raise MAP/TMP. This study study results were similar to earlier studies[39,40] as combination of Ketamine and propofol (in the ratio of 1:5) provided for better maintenance of MAP during induction of anaesthesia.

CONCLUSION

This study found out that ketofol under controlled ventilation did not increase ICP, provided better hemodynamic stability as compared to propofol alone and was comparable with propofol in quality of brain relaxation during surgery. We opine that ketofol can have an important role as an induction and maintainence agent for neurosurgical patients undergoing aneurysmal clipping. It not only can provide stable hemodynamics, good intraoperative brain conditions but also can decrease the cost of medication as ketamine is a low cost drug. Also, in this age of global warming and ensuing strict curb on the use of chlorofluorocarbons, it wont be wrong to assume that we may be looking at total ban on use of inhalational agents in the near future. Ketofol as an induction and maintenance anesthetic can provide a suitable alternative. But, larger, multicentric studies are required to study the effects of ketofol in neuroanesthesia before we can be certain of its benefits.

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