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Original Article

Anaesthesia Section

Comparison between Sevoflurane and Isoflurane for Controlled Hypotensive Anaesthesia in Patients undergoing Craniotomy for Supratentorial Intracranial Surgery: A Randomised Single-blinded Study

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ABSTRACT

Introduction: The controlled hypotensive anaesthesia technique is widely used for decades to create a bloodless surgical field and decrease intraoperative blood loss during neurosurgical procedures. Inhalation agents like isoflurane and sevoflurane provide the benefit of being hypnotic and hypotensive agents at clinical concentrations and predictable dose-dependent effects made them popular in neurosurgery.

Aim: To compare the effects of sevoflurane and isoflurane for producing controlled hypotensive anaesthesia in surgeries for supratentorial brain tumours.

Materials and Methods: The present randomised single-blind study was conducted from May 2020 to December 2021 at a teritary healthcare centre in Hyderabad, India and included 66 patients of either sex in the age group of 20-60 years, with the American Society of Anaesthesiologists (ASA) grade I and II posted for elective craniotomy for supratentorial brain tumour under general anaesthesia. Patients were randomly allocated to two aesthetic regimens: Group I received isoflurane 1 Minimum Alveolar Concentration (MAC), and Group S received sevoflurane 1 MAC. The Systolic Blood Pressure (SBP) was lowered to less than 100 mmHg before the skin incision and was maintained throughout the surgery. If the blood pressure was not maintained within the above-mentioned range, then injection propofol bolus dose of 20 mg was given intravenously. The quality of the surgical field, brain relaxation, blood loss, duration of surgery, and postoperative complications were compared. Time taken for onset and recovery of controlled hypotension and the requirement of propofol for maintaining controlled hypotension in both groups were also compared.

Results: The group S had better brain relaxation (n=26 vs n=20), less blood loss (241.5±61.62 vs 380.65±203.9 mL), and a shorter duration of surgery (135.45±25.6 vs 171.4±60.5 minutes) than group I. Group S had a few patients who required propofol (5 vs 17) to maintain controlled hypotension. The mean time for onset of hypotension and time to recovery was faster in group S (10.55±2.54 minutes) vs 15.35±0.99 minutes in group I and 12.95±3.24 minutes in group S vs 17.85±2.21 minutes in group I, respectively; p<0.001).

Conclusion: Sevoflurane is a safer and more potent drug than isoflurane to achieve controlled hypotension during surgery for a supratentorial brain tumour.

Keywords: Blood loss, Blood transfusion, Brain relaxation, Inhalational anaesthesia, Neurosurgery

INTRODUCTION

The status of brain relaxation is an important factor in anaesthesia for intracranial surgery. A relaxed brain improves operating conditions, minimises the severity of retraction injury, and prevents ischaemia from compression, which is likely to provide better patient outcomes [1,2]. Various manoeuvres are instituted to obtain brain relaxation during craniotomy. The anaesthesia technique chosen for craniotomy should be such that Cerebral Blood Volume (CBV), the Cerebral Metabolic Requirement for Oxygen ($CMRO_2$), and Cerebral Blood Flow (CBF) are minimised without compromising neuronal function. It should not interfere with cerebrovascular autoregulation and responsiveness to carbon dioxide (CO_2). It should endow the anaesthetist with the ability to rapidly and safely alter the anaesthetic depth, thereby ensuring quick, predictable recovery from the anaesthetic effects. Controlled hypotension is one of the commonly used techniques in patients undergoing craniotomy for supratentorial intracranial surgery. The concept of controlled hypotension during surgery was first proposed by Cushing in 1917 for intracranial surgery [3], and was introduced into clinical practice by Gardner WJ in 1946 [4]. Controlled hypotension is defined as 'a reduction in SBP to 80-90 mmHg (30% decrease in the SBP from the baseline blood pressure) or a decrease in the MAP to 50-65 mmHg in normotensive patients' [5,6].

The drugs used to control hypotension can be used alone (sodium nitroprusside, nitro-glycerine, trimethaphan) or in combination. Agents that can be used alone or in combination include calcium channel blockers, β-blockers, and fenoldopam. Angiotensin Converting Enzyme (ACE) inhibitors and clonidine are mainly used as adjuvants [7]. Inhalation aesthetics, isoflurane, and sevoflurane have some advantages in neurosurgery as at a low cerebral perfusion pressure (<30 mmHg), the $CMRO_2$ is better preserved and it favourably influences the global cerebral oxygen supply/demand ratio [8,9]. The use of the controlled hypotensive anaesthesia technique is based on the belief that inducing hypotension will result in brain relaxation, decreased blood loss, reduction of blood transfusion rate, satisfactory bloodless field, and shorter duration of surgery [10,11].

The primary objective of this study was to compare sevoflurane and isoflurane, producing brain relaxation in controlled hypotensive anaesthesia in craniotomy for supratentorial intracranial surgery.The secondary objective was to compare the two groups regarding the requirement of propofol to maintain controlled hypotension, onset

and recovery time of controlled hypotension, intraoperative bleeding, duration of surgery, and postoperative complications like nausea, vomiting, prolonged drowsiness, and incidence of arrhythmia.

The patients would be withdrawn from the study when they were in a triple low situation (low MAP, low BIS, and low MAC) or occurrence of any major surgical complications.

MATERIALS AND METHODS

A randomised single-blind comparative study was conducted from May 2020 to December 2021 at a tertiary healthcare centre, in Hyderabad, India. Ethical committee approval (MRIMS/2020/IEC19) and participant written informed consent were obtained.

Inclusion criteria: A total of 66 patients of ASA physical status I and II, aged between 20-60 years, of either sex with Glasgow Coma Scale 15, undergoing craniotomy for supratentorial tumour were selected for the study.

Exclusion criteria: Uncontrolled arterial hypertension, renal insufficiency, coronary artery disease, carotid insufficiency, pregnant and women on oral contraceptive pills, patients with coagulation abnormalities, or anticoagulant therapy were excluded from the study.

Sample size calculation: First 10 cases of this study was taken as pilot study and was observed that there was a 30% difference in time proportion between isoflurane and sevoflurane to achieve the target MAP (60-70 mmHg), with a power of 80% and α error of 5%. Using the Epi Info TM7 software, the calculated sample size was 55 patients. To account for a dropout rate of around 20%, 70 patients were analysed, and finally 66 patients were randomised into two groups.

A computer block randomisation with a block size of 6 was used to divide the study population into two groups of 33 each, Group S sevoflurane, and Group I isoflurane according to the inhalation agent used.

Study Procedure

All patients were premedicated with intravenous (i.v) Midazolam 0.05 mg/kg, and Glycopyrrolate 0.2 mg 20 minutes before the surgery. After instituting standard monitoring (ECG, SpO_2, BIS, invasive blood pressure with radial artery) patients were induced with propofol 2.5 mg/kg, fentanyl 2 µg/kg, and intubated with appropriate size endotracheal tube after adequate relaxation by vecuronium bromide (0.1 mg/kg). After positioning the patient, the arterial transducer was zeroed at the level of the external auditory meatus throughout the surgery. Anaesthesia was maintained with vecuronium, O_2:N_2O=1:2 (2 L/min) in a closed circuit [12], and the tidal volume (6-8 mL/kg of predicted body weight), and respiratory rate was set to maintain normocapnia with Positive End-Expiratory Pressure (PEEP) of 3-5 cm of H_2O. Group I received isoflurane 1-MAC (1.2 Vol%), Group S received sevoflurane 1-MAC (2 vol%) monitored in the expired gas analyser and the MAC was adjusted to the age and weight of the individual patient [13]. The intraoperative BIS values were kept in a range from 45 to 60. The SBP was lowered to less than 100 mmHg before the skin incision and maintained in the range of 80-100 mmHg throughout the surgery in both groups.

Surgery in all patients was performed by a single experienced surgeon. The surgeon was informed not to use any adrenaline infiltration before the skin incision. If the blood pressure was not maintained within the above-mentioned range, then propofol 20 mg boluses were used in the titration. Brain relaxation was assessed by the neurosurgeon who was blinded to the study group. The brain relaxation was simply categorised as satisfactory or not. The blood loss was replaced by Packed Red Blood Cells (PRBC) when the loss exceeded 15% of the estimated blood volume or the haematocrit below 30. The loss of blood was assessed by weighing the tetras, blood in the suction bottle, and kidney tray, after deducting the amount of irrigating fluid used during the surgery. The tetras were weighed before use and again after they were soaked with blood; the difference in weight was taken as the amount of blood loss. One gram gain in weight was taken as one mL of blood loss. The following points were specifically noted during induced hypotension in both groups:

i. **Speed of onset of hypotension:** The time taken to lower SBP to less than 90 mmHg or MAP to less than 65 mmHg was noted in both groups.

ii. **Speed of recovery from hypotension (recovery time):** The time taken for spontaneous recovery of SBP to preinduction value after discontinuation of the hypotensive agent.

The effectiveness of the hypotensive technique was judged, taking into account the following parameters:

a. Brain relaxation was satisfactory or not.

b. The number of patients who needed propofol to maintain controlled hypotension.

c. Mean intraoperative blood loss.

d. The number of patients requiring intraoperative blood transfusions.

e. Duration of surgery.

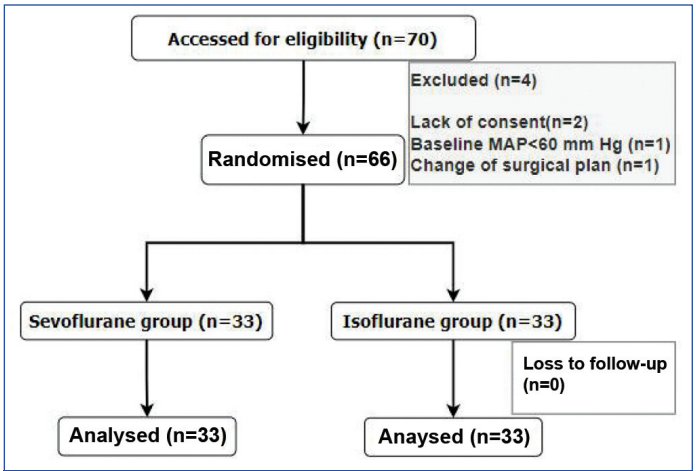
f. Incidence of postoperative complication.

STATISTICAL ANALYSIS

As appropriate, data were statistically described as mean±Standard Deviation (SD), frequencies (number of cases), and 95% confidence interval and percentages. Numerical variables between the two groups were analysed with repeated measures of Analysis of Variance (ANOVA) and compared using Student's t-test for independent samples. For analysis of categorical data, a Chi-square test was used. Pearson's correlation coefficient was applied and a $p<0.05$ was considered statistically significant. All statistical calculations were done using the Statistical Package for the Social Sciences (SPSS) software (SPSS Inc., Chicago, IL, USA) version 20.0.

RESULTS

A total of 66 patients, 33 in each group were included for the final analysis. The CONSORT flowchart is depicted in [Table/Fig-1]. Demographically both the groups were comparable with respect to age, sex, and weight [Table/Fig-2]. Preoperative haemodynamic were comparable in both groups [Table/Fig-3]. The satisfactory brain relaxation was seen more in group S (N=26) than in group I (N=20) p=0.006. The duration of surgery was significantly less in Group S than in Group I ($p<0.05$). In group S both onsets, as well as the recovery from hypotension, were faster than in group I, which was statistically significant ($p<0.001$) [Table/Fig-4]. The number of patients who required propofol in addition to the 1MAC of the inhalational agent was significantly low ($p<0.001$) in group S as compared to group I [Table/Fig-5].



[Table/Fig-1]: CONSORT flowchart.

Variables	Group S	Group I	p-value*
Age (years, Mean±SD)	51.20±5.88	47.35±16.48	0.33
Weight (kg, Mean±SD)	64.40±6.14	56.20±7.27	0.30
Sex (Males/ Female)	18/15	16/17	0.36

[Table/Fig-2]: Demographic profile.
*Analysed by two-tailed students t-test, p<0.05 significant

Haemodynamic parameters	Group S	Group I	p-value*
Heart rate (beats/minute)	75.85±8.04	78.90±14.33	0.41
Systolic blood pressure (mmHg)	126.20±10.13	126.60±7.41	0.88
Diastolic blood pressure (mmHg)	81.10±5.15	84.20±4.65	0.053
Mean arterial pressure (mmHg)	96.15±0.22	98.80±0.41	0.21
Preoperative SpO_2 (%)	98.95±0.22	98.80±0.41	0.16

[Table/Fig-3]: Preoperative vital parameters.
#Mean±standard deviation, *Analysed by two-tailed students t-test; p<0.05 significant

Quality indicators	Group S	Group I	p-value*
Brain relaxation N (%)	26 (78.78)	20 (60.6)	0.006
Duration of surgery (minutes)	135.45±25.6	171.4±60.5	<0.002
Onset of hypotension (minutes)	10.55±2.54	15.35±0.99	<0.001
Recovery from hypotension (minutes)	12.95±3.24	17.85±2.21	<0.001

[Table/Fig-4]: Quality indicators:duration of surgery, onset-recovery time, brain relaxation.
Values expressed as mean±standard deviation or number (%) *Analysed by Pearson's chi-square test and Fisher's exact test. p<0.05 significant

Propofol	Group S	Group I	p-value*
Number of patients N (%)	5 (15.1)	17 (51.5)	<0.001
Amount, mg (Mean±SD)	40±17.15	80±31.34	<0.001

[Table/Fig-5]: Propofol requirement.
*Analysed by Student's t-test; p<0.05 significant

The amount of blood loss during the surgery was significantly less in group S than group U p<0.008 [Table/Fig-6]. The number of patients who required intraoperative and postoperative blood transfusion as well as the number of units of blood was significantly more in the isoflurane group than in the sevoflurane group S p<0.05 [Table/Fig-7]. Dizziness and prolonged drowsiness (upto four hours or more) were observed more in the group I than in group S p<0.05, and the complications like nausea, vomiting, and arrhythmia were comparable in both groups [Table/Fig-8].

Variables	Group S	Group I	p-value*
Kidney tray (mL) Mean±SD	41.25±19.59	62.5±29.50	0.01
Tetra (mL) Mean±SD	42.5±16.74	66.9±23.30	0.001
Suction bottle (mL) Mean±SD	157.75±40.3	251.75±166.40	0.023
Total blood Loss (mL) Mean±SD	241.5±61.62	380.65±203.9	0.008

[Table/Fig-6]: Comparsion of blood loss in both the groups.
*Analysed by Student's t-test; p<0.05 significant

Variables	Group S	Group I	p-value*
Number of patients (N)	6	12	0.55
Number of unit intraoperative	0.25±0.44#	0.85±0.88#	0.011
Number of units intraoperative	0.10±0.31#	0.30±0.47#	0.021

[Table/Fig-7]: Blood requirement.
#Mean±standard deviation, *Analysed using Student's t-test; p<0.05 significant

Complication	Group S#	Group I#	p-value*
Nausea or vomiting	0	1 (3.03%)	0.5
Dizziness	3 (9.09%)	6 (18.2%)	0.05
Prolonged drowsiness@	1 (3.03%)	3 (9.09%)	0.005
Presence of arrhythmia	0	1 (3.03%)	0.5

[Table/Fig-8]: Post-operative complications.
#Values expressed as number (%); *analysed by chi-square test, p<0.05 significant
@drowsiness upto 4 hours or more

DISCUSSION

Brain relaxation describes the relationship between the volume of the intracranial contents and the capacity of the intracranial space when the cranium and dura are opened by the neurosurgeon. Vasodilation mediated by volatile anaesthetics occurs in a concentration-dependent manner and is the result of a direct effect on the cerebral vasculature. Sevoflurane is a less potent cerebrovascular vasodilator when administered at MAC equivalent doses and recovery is also faster with sevoflurane [11,14]. When there is less cerebral vasodilation, CBV decreases, and better brain relaxation and less intraoperative bleeding. The favourable surgical condition like relaxed brain and bloodless surgical field during sevoflurane anaesthesia gave an advantage of shorter surgical time. Duration of surgery influences outcome as time required for controlled hypotension also reduces and common severe complications like myocardial infarction, stroke, and/or acute kidney injury can be avoided [15-17]. In the present study, it was observed that the intraoperative brain relaxation was better in sevoflurane than in the isoflurane group similar to the comparative study published by Singh SK et al., in the Indian population [18]. Controlled hypotension had led to significantly less bleeding in the sevoflurane group which led to less blood transfusion in the sevoflurane group.

Soghomonyan S et al., developed a questionnaire and distributed it among Society for Neuroscience in Anaesthesiology and Critical Care (SNACC) members that addressed practice patterns related to the use of controlled hypotension [19]. There was an increased concern among the anaesthesiologists for complications associated with hypotensive anaesthesia, yet the technique is being continued to be used for more than 50% of neurosurgical procedures. It was found that inhalational agent, sevoflurane was used in 57.6%, isoflurane in 22.7%, and desflurane in 21.2% of the patients. Various methods were used by the responders to decrease the risks of hypotensive anaesthesia including hydration, maintaining adequate haematocrit, intraoperative monitoring, and limiting the time of hypotension. During controlled hypotensive anaesthesia different devices were used to monitor the integrity of cerebral perfusion e.g., Electroencephalography (EEG), BIS, evoked potential, and cerebral oximetry perioperative. In this current study, all patients were optimally hydrated, and hematocrit was maintained at around 30 during the peri-operative period. The intraoperative BIS values were kept in a range from 45 to 60. A lower BIS value of less than 45, has been independently associated with poor postoperative outcomes in several higher-risk populations. The high MAC value of anaesthetics can cause hypotension and lower BIS values which indicate deeper hypnosis and suppression of brain electrical activity. In contrast, low MAP and/or BIS in patients receiving low anaesthetic MAC value is atypical and may help identify patients who are unusually sensitive to anaesthesia and at risk for complications. Thus, the combination of low MAP, BIS, and MAC (a "triple low") may be associated with especially poor outcomes. It has been tested that a triple low of MAP, BIS, and MAC is associated with prolonged duration of hospitalisation and increased 30-day all-cause mortality [20].

Limitation(s)

This study had deliberately excluded the geriatric age group because of the associated changes in cardiovascular physiology which could have interfered with the results and analysis. Similarly, younger patients are more resistant to the action of hypotensive drugs because of an exaggerated baroreceptor response. Co-existing diseases like uncontrolled arterial hypertension, renal insufficiency, coronary artery disease, and carotid insufficiency were not included in the study as modified hypotensive anaesthesia should be used for these patients to maintain tissue perfusions [11,21]. The anaesthetist was not blinded to the study drugs as it was not possible.

CONCLUSION(S)

Sevoflurane is an effective agent for achieving controlled hypotension during supratentorial brain tumour surgeries. With specific advantages of better surgical conditions, faster induction of hypotension, decreased propofol requirement, lesser blood loss, and a faster recovery profile, sevoflurane may be a superior choice to isoflurane when induced hypotension is planned in supratentorial tumour excisions.

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