



# The comparative effects of desflurane and isoflurane on intraoperative cerebral hemodynamics, cardiovascular changes, and post-operative recovery in patients undergoing craniotomy for supratentorial tumors

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## ABSTRACT

**Background:** Preserving hemodynamic stability, providing a slack brain, and enabling early recovery are the main criteria of neuroanesthesia. The most commonly used volatile anesthetic for neurosurgeries is isoflurane due to its favorable effects on cerebral blood flow and intracranial pressure. On the other hand, desflurane, having lower blood gas partition coefficient, favors rapid recovery from anesthesia. **Aims and Objectives:** This study was conducted for comparing the effects of desflurane and isoflurane on intraoperative cerebral and cardiovascular hemodynamics and post-operative recovery among patients with supratentorial neoplasms posted for craniotomy. **Materials and Methods:** A total of 52 patients aged 20–60, ASA I and II, scheduled for craniotomy under general anesthesia, were randomized into Group I (isoflurane) and Group D (desflurane). All patients received standardized anesthetic protocol and anesthesia was maintained either with isoflurane or desflurane ( $\leq 1$  MAC). Lumbar cerebrospinal fluid pressure (LCSFP) and cerebral perfusion pressure (CPP) were monitored every 5 min till dura was opened and the degree of dural tension and brain swelling were assessed by neurosurgeons, blinded to the study, at the time of dural opening. Perioperative heart rate, mean arterial pressure, and post-operative recovery time were also noted. **Results:** No statistically significant changes were observed among two groups regarding change in LCSFP, CPP, dural tension, brain swelling, and cardiovascular changes. Post-operative recovery time was significantly shorter in desflurane group ( $P < 0.001$ ) than isoflurane group. **Conclusion:** Desflurane and isoflurane both can be used safely in maintaining neuroanesthesia. However, due to a significantly faster recovery which facilitates early post-operative neurological assessment, desflurane may be considered a better alternative to isoflurane.

**Key words:** Cerebral hemodynamics; Craniotomy; Desflurane; Isoflurane; Post-operative recovery; Supratentorial neoplasms

## INTRODUCTION

Neuroanesthesia is a challenge, in which preserving hemodynamic stability, providing a slack brain, and enabling early recovery are the main criteria.<sup>1,2</sup>

Munro-Kellie doctrine states that the cranium and its constituents, for example, blood, cerebrospinal fluid, and brain tissue, create a state of volume equilibrium, such that any increase in volume of one of the cranial constituents must be compensated by a decrease in volume of another.<sup>3</sup>

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In supratentorial tumors, with an impairment of intracranial compensatory mechanisms, intracranial pressure (ICP) tends to increase exponentially, leading to brain herniation and cerebral ischemia. This warrants constant awareness of cerebral perfusion pressure (CPP). With small changes in cerebral blood volume, considerable changes in CPP may occur.

Therefore, maintaining stable hemodynamics is important perioperatively. Unacceptable hypotension can jeopardize CPP. Similarly, perioperative hypertension can lead to intracranial hypertension, resulting in intracranial bleeding and worsening of brain oedema.<sup>4</sup>

Brain retraction pressure during operation may lead to regional cerebral dysfunction<sup>5</sup> which can be minimized by providing a slack brain, thus facilitating a good operative field.<sup>6</sup>

The ideal neuroanesthetic should maintain CPP and have no residual effects of anesthesia, thereby facilitating early post-operative evaluation of neurologic status.<sup>7</sup> Propofol has long been an ideal neuroanesthetic. Bastola *et al.*,<sup>8</sup> showed propofol to be comparable to sevoflurane and desflurane with respect to their clinical profile during neuroanesthesia in supratentorial craniotomies. Isoflurane (1-chloro-2,2,2-trifluoroethyl difluoromethyl ether) is mostly used in neuroanesthesia due to its minimal effects on cerebral blood flow  $CBF^{9,10}$  but it has a longer recovery. On the other hand, desflurane (1,2,2,2-tetrafluoroethyl difluoromethyl ether) has shorter recovery time. Early recovery accounts for one of the most principal objectives of neuroanesthesia so as to facilitate patient's early neurological assessment following craniotomy and thereafter to accelerate diagnosis followed by treatment.<sup>11</sup>

There are a few studies on the effect of desflurane on cerebral hemodynamics. Thus, in our study, we compared isoflurane with desflurane to see their effects on intraoperative changes of lumbar cerebrospinal fluid pressure (LCSFP), CPP (CPP=Mean Arterial Pressure [MAP]-ICP), degree of dural tension, brain swelling, perioperative hemodynamics (heart rate [HR] and MAP), and post-operative recovery (including emergence and extubation time and time taken to obtain modified Aldrete score  $\geq 9$ ).

### Aims and objectives

This study was conducted for comparing the effects of desflurane and isoflurane on intraoperative cerebral and cardiovascular hemodynamics and post-operative recovery among patients with supratentorial neoplasms posted for craniotomy.

## MATERIALS AND METHODS

On receiving clearance from the Institutional Ethics Committee, CTRI/2018/09/015570 and written informed consent, this open-label, parallel group, randomized controlled trial was carried out in Bangur Institute of Neurosciences, Institute of Postgraduate Medical Education and Research, Kolkata, between March 2017 and August 2018. Fifty-two adult patients with age between 20 and 60 years, ASA I and II, having Glasgow Coma Scale 15 undergoing elective craniotomy under general anesthesia for supratentorial tumors, were randomized into Group I (receiving isoflurane) and Group D (receiving desflurane) using a computer-based random number generator in permuted blocks of varying sizes. This assignment was kept in sealed envelopes which were not disclosed till receipt of informed consent.

For calculating sample size, LCSFP changes were considered as the primary outcome measure. Twenty-three subjects would be required per group in order to detect the difference of 5 mmHg in LCSFP between the groups with 80% power and 5% probability of Type 1 error. This calculation assumed SD of 6 mmHg in LCSFP and two-sided testing. Considering a 10% dropout, actual number of subjects recruited would be 26 per group with the overall target of 52. Sample size calculation was done by nMaster 2.0 (Department of Biostatistics, CMC-Vellore) software.

Patients with a history of significant pulmonary, cardiovascular, renal, hepatic, endocrine, or muscular disorders; allergic to any anesthetic drug; having tumors with midline shift; surgery associated complications such as injury to the vessels or vital structures or massive intraoperative bleeding requiring elective post-operative mechanical ventilation; and those exposed to general anesthesia in preceding 7 days were excluded from the study.

Patients were fasted as per standard guidelines. In the operation theater, non-invasive blood pressure, electrocardiogram, pulse oximetry, nasopharyngeal temperature probe, and capnogram were attached and baseline vitals were recorded. Intravenous lines were secured. Before induction of anesthesia, insertion of an arterial catheter was done for continuously measuring arterial blood pressure.

Same anesthetic techniques were followed in every patient. Anesthesia was induced with sodium thiopentone up to 5 mg/kg, rocuronium 0.8 mg/kg, and fentanyl 2  $\mu$ g/kg. After endotracheal intubation, tidal volume was set at 6–8 ml/kg and  $EtCO_2$  maintained between 28 and 32 mmHg. Low-flow technique with a gas flow of 1 L/min with 50%  $O_2$  and

N<sub>2</sub>O was followed. Arterial blood gas analysis was done at intervals to correlate PaCO<sub>2</sub> with EtCO<sub>2</sub> and to maintain PaO<sub>2</sub> between 100 and 200 mmHg. Anesthesia was then maintained with an infusion of propofol 100 mcg/kg/min until insertion of a subarachnoid catheter with the help of an 18-gauge Tuohy-Schiff needle. Utmost care was taken to prevent any CSF loss. Throughout study period, LCSFP was measured at midcranial level with the zero reference and with the help of a pressure transducer. Communicating CSF system was confirmed at the start by an increase in LCSFP on elevation of the patient's head and was reconfirmed at the end of the recording period by noting the direct response to digital pressure on the dura. LCSFP, HR, MAP, EtCO<sub>2</sub>, SpO<sub>2</sub>, and CPP were continuously monitored. LCSFP, CPP, HR, and MAP were recorded every 5 min until the opening of the dura, and thereafter, MAP and HR were recorded every 15 min until 1 h postoperatively. Monitoring of muscle relaxation was done throughout anesthesia by neuromuscular monitor with TOF maintained at  $\leq 2$ . MAC values were observed continuously in both the groups.

The scalp over the operative field and the points of attachment of Mayfield head holder onto the head of the patient were infiltrated with 1% lignocaine.

Maintenance of anesthesia was done by intravenous infusion of rocuronium at 9–12  $\mu$ g/kg/min and administration of inhalational anesthetics (either isoflurane, or desflurane, depending on study group) was maintained at  $\leq 1$  MAC. Dose of inhalational anesthetics and fentanyl at 0.5  $\mu$ g/kg/h was subsequently adjusted to maintain HR and MAP within a range of 20% of pre-anesthesia levels.

Tachycardia or hypertension persisting for more than 1 min (defined as HR or MAP increasing to  $>20\%$  of pre-anesthesia value) and not responding even after use of maximal permitted anesthetic concentration was managed by giving labetalol 25 mg intravenous bolus.

Incidents of hypotension (MAP decreasing to  $<20\%$  of the pre-anesthesia values) not resolving even after intraoperative replacement of fluids was treated using vasopressor (phenylephrine 0.5–1 mcg/kg iv). Bradycardia (HR decreasing to  $<20\%$  of pre-anesthesia value) and persisting for more than 1 min was managed with atropine sulfate 0.02 mg/kg IV. These events of hemodynamic alterations were noted and informed to the neurosurgeon.

Normothermia during operation was maintained actively with Bair-Hugger and body temperature was continuously monitored.

The neurosurgeon, blinded to the study group, assessed dural tension at the time of dural opening through tactile

evaluation which was categorized as very slack, normal, increased tension, and pronounced increased tension and the degree of brain swelling visually, which was also assessed and scored as: 1=No swelling; 2=Moderate brain swelling; and 3=Pronounced brain swelling. Injection mannitol 0.75 g/kg was infused in both the groups after the assessment of dural tension and brain swelling.

At the time of hemostasis, N<sub>2</sub>O was discontinued. During securing the bone flap, rocuronium was stopped. Neostigmine at 50  $\mu$ g/kg and glycopyrrolate at 10  $\mu$ g/kg were used to reverse neuromuscular block at a TOF ratio 0.9. After skin closure and the dressings were in place, inhalational anesthesia was stopped. To accelerate anesthetic washout, increase of fresh gas flow was done to a value which was equal to minute volume.

Recovery time was measured as emergence time (time being calculated from the stop of inhalational anesthesia to eye opening of the patient) and extubation time (time being calculated from the stop of inhalational anesthesia to extubation of the patient). Extubation was done when there was adequate respiratory function (frequency 10–25 breaths/min; tidal volume  $>5$  ml/kg; and SpO<sub>2</sub>  $>95\%$ ), stable hemodynamics, and fully recovered upper airway reflexes. Post-extubation patients were shifted to the post-anesthesia care unit (PACU). They got paracetamol 15 mg/kg IV and supplemental oxygen at 6–8 L/min (FiO<sub>2</sub> 40%) was provided throughout the period of observation. The time required to obtain modified Aldrete score  $\geq 9$  was observed.

Dr. Jorge Antonio Aldrete<sup>12</sup> developed a scoring system for discharge of the patients from PACU which was later named after him as Aldrete scoring. It includes:

1. Activity
2. Respiration
3. Circulation
4. Consciousness
5. O<sub>2</sub> saturation

**Activity: Defined as ability to move voluntarily or on command**

	Score
Four extremities	2
Two extremities	1
Zero extremities	0

**Respiration**

	Score
Able to breath and cough freely	2
Dyspnea, shallow, or limited breathing	1
Apneic	0

## Circulation

	Score
BP±20 mmHg of pre-anesthetic level	2
BP±20–50 mmHg of pre-anesthetic level	1
BP±50 mmHg of pre-anesthetic level	0

## Consciousness

	Score
Fully awake	2
Arousable on calling	1
Not responding	0

## O<sub>2</sub> Saturation

	Score
Maintain SO <sub>2</sub> >92% on room air	2
Needs O <sub>2</sub> to maintain SO <sub>2</sub> >90%	1
SO <sub>2</sub> <90% even with O <sub>2</sub> supply	0

A score of 9 indicates that a patient is fit to be discharged from the PACU.

Data were summarized by routine descriptive statistics, namely, mean and standard deviation for numerical variables that were normally distributed, median and interquartile range for skewed numerical variables, and counts and percentages for categorical variables. Numerical variables were compared between groups by Student's independent samples t-test, if normally distributed, or by Mann–Whitney U- test, if otherwise. Fisher's exact test or Pearson's Chi-square test was employed for intergroup comparison of categorical variables. Analyses was two tailed and statistical significance level was set at  $P<0.05$  for all comparisons.

## RESULTS

Out of 52 patients posted for supratentorial craniotomy, six patients were excluded as the LCSFP could not be measured because of inability to place the lumbar catheter in two patients and intraoperative displacement/compression of the catheter in four patients. CONSORT flow diagram showing the patients at every stage of the trial is shown in Figure 1. The patients were monitored for intraoperative cerebral hemodynamics, perioperative cardiovascular changes, and post-operative recovery.

The demographic data (age, gender, and ASA status) are shown in Table 1. They were found to be comparable in both the groups ( $P>0.05$ ) (Table 1).

Values are presented as mean and standard deviation for numerical variables that were normally distributed; and counts and percentages for categorical variables. Comparison of age among groups was made by Student's independent samples t-test and comparison of gender

**Table 1: Demographic profile of patients**

Parameters	Isoflurane	Desflurane	P value
Age (in years) mean±SD	36.39±9.3066	37.74±11.902	0.671
Gender (M/F)	(11/12)	(11/12)	1.000
ASA-PS (I/II)	(14/9)	(14/9)	1.000

SD: Standard deviation, ASA-PS: American Society of Anesthesiologists Physical Status

and ASA status between groups was done using Fisher's exact test.

Dural tension between the groups was insignificant statistically ( $P=0.916$ ) (Table 2). Out of 23 patients in each group, three in Group I and four in Group D had pronounced increased dural tension. One patient in each group had normal dural tension whereas rest had increased dural tension.

In both groups, intraoperative degree of brain swelling was comparable ( $P=1.000$ ) (Table 2). Two patients in each group had pronounced brain swelling (Grade 3); rest had moderate degree of brain swelling (Grade 2).

Values are presented as counts and percentages for categorical variables. Comparison of dural tension between groups was done using Pearson's Chi-square test and comparison of degree of brain swelling among the groups was achieved using Fisher's exact test.

LCSFP did not differ significantly between the two groups at any time during surgery ( $P>0.05$ ) (Figure 2).

Changes in LCSFP among the groups were compared using Student's independent samples t-test.

Mean CPP was not significantly different among the two groups ( $P>0.05$ ) (Figure 3).

Changes in CPP among the groups were compared using Student's independent samples t-test.

MAP (Figure 4) and HR were maintained within 20% of pre-anesthesia levels and were comparable in both groups at different perioperative time interval.

Changes in MAP among the groups were compared using Student's independent sample t-test.

Statistically significant difference in recovery variables was found ( $P<0.001$ ) (Table 3). Mean time to eye opening was 8.13 min in Group I and 5.17 min in Group D, mean time to extubation was 12 min in Group I and 8.87 min in Group D, and mean time to obtain modified Aldrete score  $\geq 9$  was 16.65 min in Group I and 12.70 min in Group D.

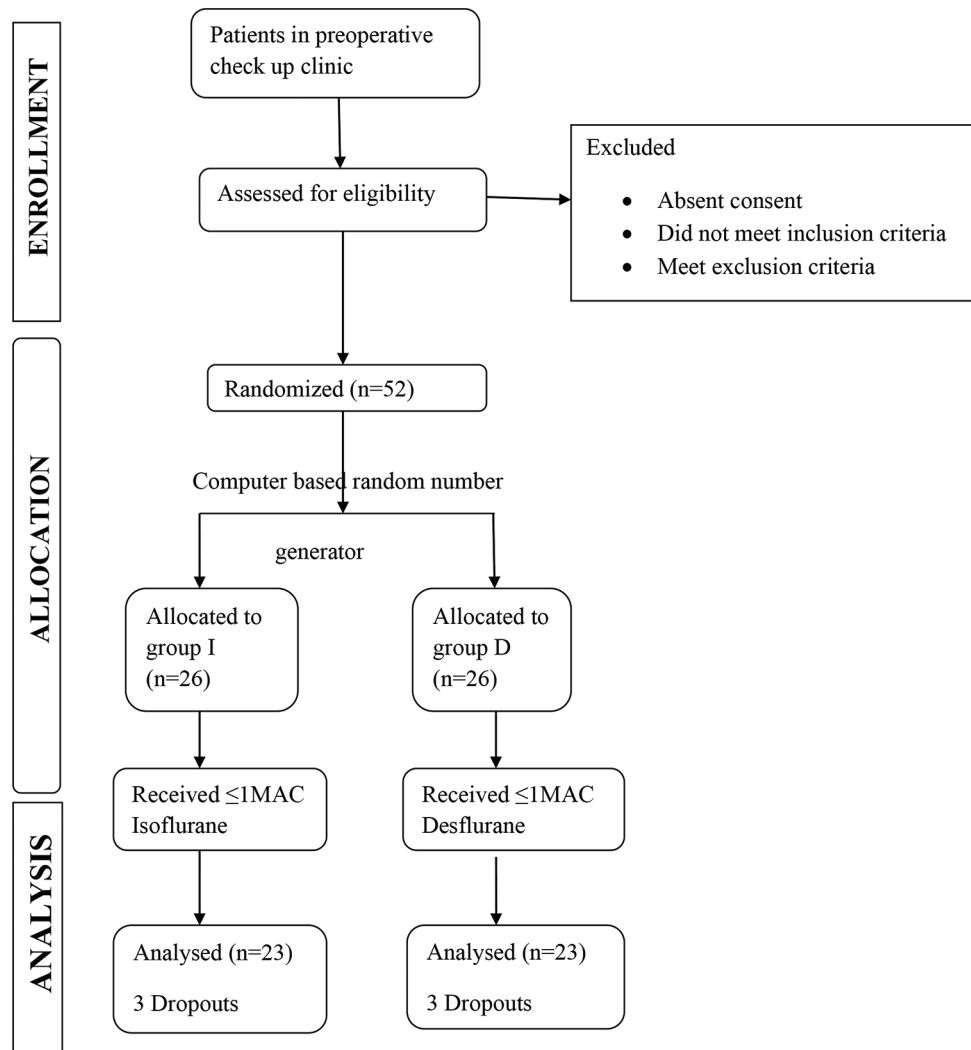


Figure 1: Consort flow diagram of the study

Table 2: Degree of dural tension and brain swelling among the study population

	Degree of dural tension			Degree of brain swelling		
	Normal	Increased	Pronounced increased	Grade 1	Grade 2	Grade 3
Isoflurane	1 (4.35%)	19 (82.61%)	3 (13.04%)	0	21 (91.30%)	2 (8.70%)
Desflurane	1 (4.35%)	18 (78.26%)	4 (17.39%)	0	21 (91.30%)	2 (8.70%)
P value		0.916			1.000	

Values are presented as median and interquartile range (Q1, Q3) for skewed numerical variables. Recovery characteristics (time to eye opening, time to extubation, and time taken to obtain modified Aldrete score  $\geq 9$ ) were compared between the two groups using Mann-Whitney U-test.

## DISCUSSION

In this study, isoflurane and desflurane were compared for maintaining anesthesia because of the availability and accessibility of monitoring of end-tidal agent, ease of

administration, and predictable intraoperative and recovery properties.<sup>13</sup>

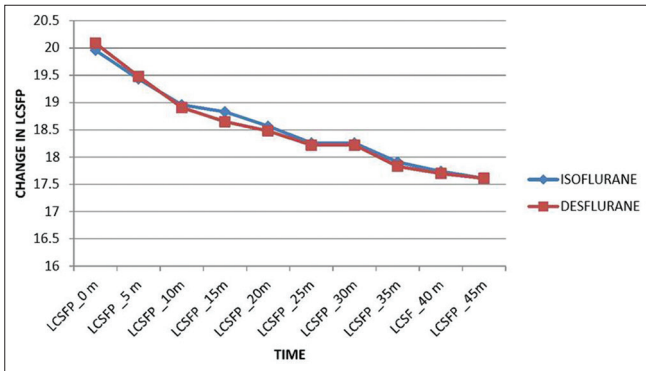
Isoflurane is widely used in neuroanesthesia practice but with prolonged recovery (blood gas partition coefficient is 1.4).

There is debate on using desflurane in neurosurgical procedures because it has vasodilatory effect on cerebral blood vessels. On the other hand, desflurane has an early recovery due to a lower blood solubility, blood gas (0.42), and tissue blood partition coefficients with a wake up time

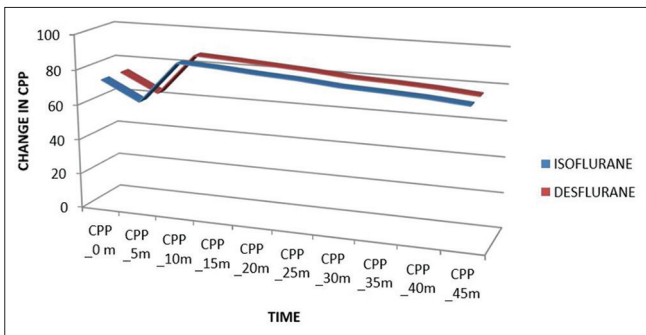
**Table 3: Recovery characteristics among the study population**

Recovery parameters (in min)	Isoflurane			Desflurane			P value
	Mean	Median	Interquartile range (q3–q1)	Mean	Median	Interquartile range (q3–q1)	
TIME EYEOPEN	8.13	8.00	9.00–8.00	5.17	5.00	6.00–5.00	<0.001
TIME EXTUB	12	12	13.00–12.00	8.87	9.00	9.00–8.00	<0.001
TIME ALDRETE9	16.65	17	17.00–16.00	12.70	13.00	13.00–12.00	<0.001

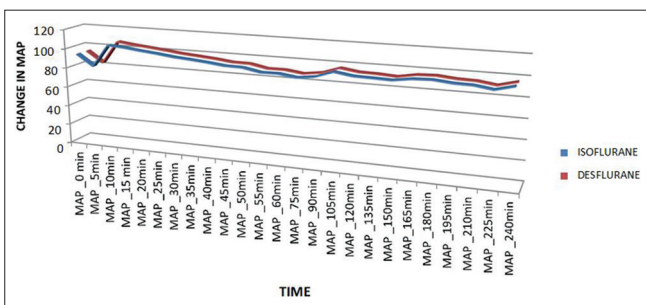
TIME EYEOPEN: Time to eye opening, TIME EXTUB: Time to extubation, TIME ALDRETE9: Time taken to obtain modified Aldrete score $\geq$ 9



**Figure 2:** Changes in lumbar cerebrospinal fluid pressure between two groups. LCSFP: Lumbar cerebrospinal fluid pressure



**Figure 3:** Changes in cerebral perfusion pressure between two groups. CPP: Cerebral perfusion pressure



**Figure 4:** Changes in mean arterial pressure among the study population. MAP: Mean arterial pressure

approximately 50% less than those observed following isoflurane. Sharma and Jangra,<sup>14</sup> concluded that desflurane is a very useful inhalational drug for maintaining neuroanesthesia, the most important benefit being fastest recovery time. In addition, it has distinct advantage in

obese, elderly, and renal-compromised patients with an emerging benefit of usefulness in neuromonitoring.

The present study demonstrated that LCSFP (Figure 2) and CPP (Figure 3) were not significantly different at any time between isoflurane and desflurane administered at  $\leq 1$  MAC with EtCO<sub>2</sub> maintaining between 28 and 32 mmHg.

Increased brain retraction pressure correlates with the incidence of regional cerebral dysfunction.<sup>15</sup> Thus, good brain relaxation is needed during surgery. In our study, intraoperative dural tension and brain swelling (Table 2) were found to be comparable in both groups. Pronounced brain swelling (Grade 3) as observed in two patients in each group was reduced after receiving extra dose of mannitol 0.5 mg/kg.

Fraga et al.,<sup>16</sup> found that there were no differences in ICP as patients were anesthetized with 1 MAC of either isoflurane or desflurane. Cerebral AVDO<sub>2</sub> and CPP were found to be decreased with both agents. Todd et al.,<sup>17</sup> could not demonstrate the supremacy of one anesthetic over other among propofol, isoflurane, and fentanyl with respect to either decrease in ICP or improvement of brain relaxation scores in patients scheduled for supratentorial craniotomy.

Kaye et al.,<sup>7</sup> found that in patients undergoing craniotomy, isoflurane and desflurane at 1.2 MAC have similar effects on MAP and CPP. Ornstein et al.,<sup>18</sup> conducted studies which also showed similar results. However, Muzzi et al.,<sup>19</sup> found that in hypocapnic neurosurgical patients having supratentorial mass, there is an increase in CSFP after administering 1 MAC desflurane in comparison to 1 MAC isoflurane. However, at 0.5 MAC of desflurane and isoflurane, he found no difference in CSFP. Whereas Talke et al.,<sup>20</sup> found that in normocapnic patients scheduled for transsphenoidal hypophysectomy, use of both isoflurane and desflurane at 0.5 and 1.0 MAC resulted in an increase in LCSFP.

In this study, MAP (Figure 4) and HR were maintained within 20% of pre-anesthesia levels and were comparable in both groups at different perioperative time intervals. Thus, CPP did not change significantly. Dupont et al.,<sup>21</sup> also showed no significant differences in hemodynamic

variables as patients posted for elective lobectomy or pneumonectomy were anesthetized with either isoflurane or desflurane.

Recovery characteristics in the present study were evaluated as emergence and extubation time and time to obtain modified Aldrete score  $\geq 9$  (Table 3). These were significantly shorter in the desflurane group in comparison to those in the isoflurane group. In agreement with these findings, Paul *et al.*,<sup>22</sup> found that desflurane significantly reduced emergence times, thereby facilitating an early neurological examination for patient. Kaye *et al.*,<sup>7</sup> reported that neurosurgical patients when anesthetized with desflurane opened their eyes and obeyed commands 50% faster than those receiving isoflurane. Similar results were also found by different authors.<sup>13,23-26</sup> A study conducted by Chahar *et al.*,<sup>27</sup> found that both desflurane and isoflurane can be used in patients undergoing supratentorial craniotomy with desflurane having added advantage of faster post-operative recovery and emergence characteristics. Although both desflurane and isoflurane had comparable brain relaxation grades, 23 patients in desflurane group had Grade 1 brain swelling in comparison to 18 patients in isoflurane group ( $P=0.35$ ).

Inserting intraventricular catheter is the most accurate ICP monitoring method. The intraventricular catheter is costly and measuring ICP by it during the operation becomes very difficult to carry out. Thus, in this study, LCSFP was correlated with ICP as Lenfeldt *et al.*,<sup>28</sup> found that lumbar space ICP correlated excellently to ICP in brain tissue in patients having communicating CSF systems. Our patients also had communicating CSF systems. This was confirmed by an increase in LCSFP on elevation of the patients' heads after insertion of the catheter.

### Limitations of the study

This study has limitations. Intraoperative degree of dural tension and brain swelling assessed by the neurosurgeon were majorly subjective. Depth of anesthesia could not be assessed due to difficulty in keeping the BIS electrodes over the patients' foreheads due to scrubbing. We used nitrous oxide instead of air. It was not possible to double blind this study as the monitors showed which inhalational anesthesia was being used. Desflurane has a higher cost as compared to isoflurane though both are available free in our institution and to minimize the use, we used low-flow techniques.

## CONCLUSION

Both desflurane and isoflurane in this study appeared to serve the objectives of preserving hemodynamic stability and producing adequate brain condition in intracranial

operations. Thus, both can be used safely in maintenance of neuroanesthesia. However, due to a statistically significant faster recovery which facilitates early post-operative neurological assessment, desflurane may be considered a better alternative to isoflurane.

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**Authors Contribution:**

**TM**- Design of the study, acquisition of data, statistical analysis and interpretation of data, preparation of manuscript, and revision of the manuscript;  
**MM**- Interpreted the results, reviewed the literature, manuscript preparation, and coordination; **AA**- Concept and design of the study, formulated study objectives, planned the analysis, interpreted the results, and reviewed the literature; and **SC**- Interpreted the results, reviewed the literature, manuscript preparation, and coordination.

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