Intravenous versus inhalational anesthesia trial for outcome following intracranial aneurysm surgery: A prospective randomized controlled study

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**ABSTRACT**

**Background:** For maintenance of anesthesia for intracranial aneurysmal neck clipping, both intravenous and inhalational anesthetics are in vogue. We aimed to evaluate the superiority of one agent over the other for long-term neurological outcomes in these patients.

**Methods:** This prospective assessor-blind randomized study was conducted in 106 patients of 18–65 years of age with World Federation of Neurosurgeons Grade I-II of subarachnoid hemorrhage. After written informed consent, the patients were randomized into – intravenous group (Propofol) and inhalational group (Desflurane). The primary outcome was to study neurological outcome using Glasgow outcome scale (GOS) at 3 months following discharge while secondary outcomes included intraoperative brain condition, intraoperative hemodynamics, duration of hospital stay, Modified Rankin Score (MRS) at discharge and 3 months, and Barthel Index at 3 months following discharge and estimation of perioperative biomarkers of brain injury.

**Results:** The GOS at 3 months was 5 (5.00–5.00) in the propofol group and 5 (4.00–5.00) in the desflurane group (P = 0.24). Both the anesthetics were similar in terms of intraoperative hemodynamics, brain relaxation, duration of hospital stay, MRS at discharge and 3 months, and Barthel Index at 3 months (P > 0.05). The perioperative serum interleukin-6 and S100B were comparable among the groups (P > 0.05).

**Conclusion:** The long-term neurological outcome of good grade aneurysm patients undergoing craniotomy and clipping remains comparable with the use of either propofol or desflurane. The effect of the two anesthetic agents on the various clinical parameters and the biomarkers of brain injury is also similar.

**Keywords:** Aneurysmal subarachnoid hemorrhage, Desflurane, Neurological outcome, Neuronal injury, Propofol

**INTRODUCTION**

Aneurysmal subarachnoid hemorrhage (SAH), an alarming cause of hemorrhagic stroke, results from a breach in dilated intracranial blood vessel walls causing collection of blood in
the subarachnoid space. With only 30% of patients being able to return to independent living, it poses an alarming health care liability.[13] Early intracranial clipping of an aneurysm is an intricate and extensive procedure entailing an anesthetic technique that allows for maintenance of cerebral perfusion pressure (CPP), optimum brain relaxation, and reduction of transmural pressure with an early awakening. In neurosurgical procedures, both intravenous and volatile anesthetics are commonly being used for the maintenance of anesthesia, but speculation regarding the supremacy of one agent over the other persists.[1,3] Propofol reduces cerebral blood flow (CBF) as well as the cerebral metabolic rate of oxygen consumption (CMRO₂) and offers neuroprotection.[6,14] Desflurane reduces CMRO₂ but may not result in a corresponding decline in CBF.[1,9]

A study analyzing perioperative outcomes using burst suppression dosages of propofol and desflurane reported identical brain conditions and awakening times in patients posted for clipping following aneurysmal SAH.[4] Another randomized controlled trial (RCT) conducted on 70 patients found propofol and desflurane to be comparable regarding postoperative morbidity in patients undergoing aneurysmal clipping. This study described the short-term outcome as regards to Glasgow Coma Scale (GCS) of the patient and the presence of any new neurological deficit 24 h following surgery.[12] Hoffman et al. have compared the effects of etomidate and desflurane in patients undergoing middle cerebral artery occlusion for >15 min. In their study, tissue hypoxia and acidosis were observed during etomidate treatment. The use of desflurane for brain protection significantly increased brain tissue oxygen pressure and inhibited acidosis during prolonged middle cerebral artery occlusion.[5]

Propofol and desflurane used intraoperatively have variable effects on cerebral vasomotor tone. Whether intraoperative use of anesthetics can categorically influence long-term outcomes after aneurysm surgery remains uncertain. The ideal anesthetic agent for patients undergoing aneurysm surgery is not yet known. Very limited prospective data regarding the long-term impact of anesthetic agents on patients undergoing microvascular clipping following aneurysmal SAH exists. With this background, we hypothesize that there could be a difference in the long-term neurological outcome of patients with the use of propofol when compared to the desflurane in patients undergoing surgery for aneurysmal SAH. This study aimed to evaluate the difference in the long-term neurological outcome of patients undergoing microsurgical clipping with the use of propofol as compared to desflurane. The neurological outcome using Glasgow outcome scale (GOS) at 3 months following discharge was the primary outcome while intraoperative brain condition, intraoperative hemodynamics, duration of hospital stay, Modified Rankin Score (mRS) at discharge, mRS and Barthel's index at 3 months following discharge and the estimation of perioperative biomarkers of brain injury were the secondary outcomes of the study.

MATERIALS AND METHODS

This prospective assessor-blind RCT was conducted from February 2015 to December 2016 in the Division of Neuroanesthesia, Department of Anesthesia and Intensive Care, Postgraduate Institute of Medical Education and Research, Chandigarh, India. Institutional ethics committee approval was sought (NK/1460/Res/1096) and the trial was registered with Clinical Trials Registry, India (CTRI/2015/04/005684). Patients aged 18–65 years with World Federation of Neurosurgeons (WFNS) Grade I–II of SAH were recruited after written informed consent. Exclusion criteria were pregnancy, presence of coronary artery disease, chronic obstructive pulmonary disease, hepatic, or renal dysfunction. Any adverse intraoperative event causing major hemodynamic instability due to massive hemorrhage or severe brain bulge prohibiting replacement of bone flap during craniotomy closure also led to exclusion of that patient from the study.

Randomization and blinding

One hundred and six patients undergoing aneurysmal neck clipping after spontaneous intracranial aneurysm rupture were randomized using computer-generated random numbers into - the intravenous group (Group IV: receiving Propofol) or the inhalational group (Group IH: receiving Desflurane). The patients, surgeons, and nurses involved in the study were blinded to group allocation. The anesthesiologist managing the case in operation theatre did the intraoperative data recording and could not be blinded to the anesthetic agent used. He was not part of further study. Further, the Junior Research Fellow who did the postoperative data recording and analysis was blinded to the group assigned to the patients.

Anesthesia protocol

The preanesthetic clinical, biochemical, and radiological parameters of the patients were recorded. Intraoperatively, standard American Society of Anesthesiologist monitors in the form of electrocardiogram, pulse oximeter, and noninvasive blood pressure were attached. Patients received fentanyl 2 mcg/kg before induction followed by 0.5–2 mcg/kg/h as infusion. Propofol titrated to loss of verbal response was used as an induction agent in both groups. Vecuronium (0.1 mg/kg) was used to facilitate tracheal intubation and subsequently administered as boluses to maintain less than two twitch response on neurostimulation. Anesthesia was
maintained with oxygen and medical air (1:1) with propofol infusion or desflurane as maintenance agent as per the group assigned to maintain Bispectral index (BIS) value between 40 and 60. Intraoperatively, 0.9% saline was used as maintenance fluid. Mannitol 0.5 gm/kg was given in both groups. Patients were kept normothermic (36–37°C) using a forced-air warming blanket. The surgery was conducted by experienced neurosurgeons who were not aware of the anesthetic agent being used for maintenance of the anesthesia.

At the start of skin closure, fentanyl infusion was stopped, whereas the anesthetic agents were discontinued following completion of skin closure. Tracheal extubation was carried out as per the clinical judgment of the attending anesthesiologist. The postoperative management was at the discretion of the neurosurgical and intensive care team.

**Study protocol**

Glasgow outcome score (GOS) at 3 months following discharge was the primary outcome measured. GOS 5 being no or mild disability and GOS 1 being death. Intraoperative brain condition, intraoperative hemodynamics, duration of hospital stay, mRS at discharge, mRS, and Barthel's index at 3 months following discharge, and the estimation of perioperative biomarkers of brain injury (S100B and interleukin-6 [IL6]) were the secondary outcomes of the study.

The degree of brain swelling was assessed at the time of dural opening by the operating surgeon who was not aware of the maintenance anesthetic agent. Brain relaxation grades were: Grade 1 – relaxed brain, Grade 2 – a tense brain with mild but acceptable brain swelling, Grade 3 – a tight brain with moderate brain swelling requiring no definite change in management, and Grade 4 – bulging brain with severe swelling requiring some definite change in management (e.g. administration of supplementary doses of mannitol, boluses of propofol, etc.).[6] The biochemical markers of neurological injury (S 100 ß and IL6) were measured preoperatively, intraoperatively and postoperatively using an enzyme-linked immune sorbent assay (ELISA) reader (Erba Lisa Scan II, Germany), S100B (YH Biotech Co., Shanghai, China), and IL6 (Ray Biotech, GA, USA). The duration of hospital stay was noted and compared among the two groups.

**Statistical analysis**

**Phase-I**

The collected data were entered into Microsoft Excel®. The entered raw data served as the base for the master sheet. A copy of raw data was generated and used for further cleaning and analysis purpose. To protect the privacy of the patients, we de-identified data as per appropriate modification of Health Insurance Portability and Accountability Act guidelines as per Indian settings.[10]

Subsequently, the dataset was cleaned and assessed for cosmetic and logical errors. Further, a data dictionary was prepared to aid data analysis and interpretation. Finally, the master sheet along with the data dictionary was protected with a password.

**Phase-II**

The master sheet prepared in phase-I was used to report descriptive and inferential statistics. The categorical and quantitative data were appropriately reported with frequency (%) and mean (SD) or median (IQR), respectively. Subsequently, the normality of quantitative data was assessed using Shapiro–Wilk. The quantitative data were further analyzed using an unpaired t-test and Mann–Whitney test after validating the assumptions. Chi-square test or Fisher’s exact test were applied for categorical data. The criteria to run a multivariable model for variables with \( P \leq 0.10 \) were not met by variables in the univariate stage. Therefore, we did not apply a multivariable model. A 2-tailed \( P < 0.05 \) was used to declare statistical significance for all the analyses.

**Sample size**

Considering the postoperative outcome data of a recent study conducted at the Department of Neurosurgery, PGIMER, the incidence of good outcome (GOS 4 and 5) in patients (WFNS grade I and II) postaneurysmal SAH surgery was 59%. In a similar group of patients, the incidence of poor outcomes (GOS 1, 2, and 3) was 27%.[14] The difference between the incidence of a good outcome and a poor outcome was 32%. Assuming that the use of anesthetics would increase this difference in outcome by twice the prevailing incidence, the calculated sample size for a statistical power of 80% and a two-sided alpha of 0.05 was 46 per group. Taking into account the 20% drop-out rate due to surgical complications the sample size was increased to 53 per group. This sample size was calculated using G Power 3.1.7 calculators for binary outcome superiority trial from the website www.sealedenvelope.com (accessed on August 27, 2013).

**RESULTS**

The patient characteristics and recruitment flow has been shown in the Consort diagram [Figure 1]. Out of 106 patients who were enrolled in the study, 15 patients were excluded and 44 patients in the propofol group and 47 patients in the desflurane group (total 91 patients) were finally analyzed. Demographics and preoperative characteristics were similar in both the groups [Table 1]. No notable difference in intraoperative variables such as duration of anesthesia, total temporary clipping time, intraoperative hemodynamics, and
brain relaxation score between both the groups was observed [Table 2]. Median hospital stay in the propofol group and desflurane group were comparable. The condition of the patient at discharge was assessed in both the groups using mRS, the median value being zero in the propofol group and one in the desflurane group, the difference, however, was statistically insignificant [Table 3].

GOS at 3 months following discharge was the primary outcome measured. The median GOS was 5 in both groups making it statistically insignificant. Comparison of mRS at 3 months after discharge revealed no significant difference between the two groups, the median value being zero. The Barthel index at 3 months with a median value of 100 in both the groups was statistically insignificant [Table 3].

**DISCUSSION**

The query regarding the optimum agent for maintenance of anesthesia during aneurysmal clipping surgery remains unresolved. There is a bias toward the use of intravenous anesthetics in neurosurgical patients. [6,12] Nevertheless, both desflurane and propofol are routinely used for anesthetic management during intracranial surgery. Although the short-term outcome with the use of propofol and desflurane has recently been studied, there are limited data regarding the effect of anesthetics on brain biochemical milieu and the long-term neurological outcome after surgery following aneurysmal SAH. [2,7] The purpose of the present trial was to determine whether we, as neuroanesthesiologists, by choosing suitable maintenance agents can influence long-term neurological outcomes after aneurysmal clipping surgery.

Propofol is a rapid-acting intravenous anesthetic agent that potentiates gamma-aminobutyric acid A receptor activity. It possesses the benefit of a short duration of action, rapid titrability, less postoperative nausea and vomiting along with
rapid emergence. Intravenous administration leads to dose-dependent cerebral vasoconstriction and hence fall in CBF, CMRO, and any preexisting cerebral edema. There is concern about the propofol-induced decrease in CPP through its hypotensive effect. It may be speculated that cerebral vasoconstriction in the face of raised intracranial pressure (ICP) may add to the ongoing ischemia. Desflurane with a low blood-gas partition coefficient of 0.42 is the present-day contestant in the volatile anesthetic group. Like propofol, it also decreases CMRO, but the effect on CBF depends on the dose used. At one minimum alveolar concentration (MAC), it decreases CMR and hence CBF while preserving cerebrovascular reactivity. There is an apprehension about the direct cerebral vasodilatory property of desflurane at >1.5 MAC which may increase ICP in vulnerable patients. However, one may surmise that the cerebral vasodilatation may benefit the patients predisposed to a common complication of cerebral vasospasm following SAH. Despite the differences in the neurophysiological properties of these anesthetics, there is a paucity of evidence regarding the
efficacy of one anesthetic over the other for long-term outcomes in patients undergoing aneurysmal neck clipping.

Aneurysmal SAH is not a solitary event and patients who survive the initial insult face long-lasting physical and cognitive deficits. Hence, investigating the long-term outcome seems reasonable. The results of our study indicate that there is no difference in the long-term neurological outcome and postanesthetic morbidity with the use of propofol or desflurane. Lee et al. have studied the effect of the use of propofol and desflurane in aneurysmal clipping surgery and found no effect of the anesthetic agent on GCS on day 14 and GOS at 3 months after surgery between the two groups.\(^4\) Our results correspond with the above study with the median GOS at 3 months being comparable in both groups. Comparison of mRS at 3 months after discharge to assess recovery of functions after initial aneurysmal rupture revealed no notable difference between the two groups. Similarly, performance in activities of daily living as measured by the Barthel index was similar in both groups at 3 months. Hence, no discernible difference in the long-term neurological outcome with the use of either propofol or desflurane was noted in our study. This indicates that despite the variable neuropharmacological profile of the two drugs, their effect on long-term neurological outcome in good grade aneurysm patients (WFNS Grade I–II) is not different.

Our study also indicates no difference in the short-term neurological outcome with the use of either propofol or desflurane. An RCT conducted on 70 patients assessing propofol and desflurane for postanesthetic morbidity in patients undergoing aneurysmal clipping found both to be comparable.\(^2\) Length of postoperative hospital stay was taken as an indicator of short-term outcome in the above study. In our study, duration of hospital stay and mRS at discharge was comparable to this study, thereby indicating that both propofol and desflurane have a similar short-term outcome. A tense brain thwarts the accessibility of the aneurysmal neck for clipping by the neurosurgeon. Intraoperative brain relaxation is one of the imperative goals of anesthetic management. Our study did not demonstrate a marked difference in brain relaxation with the use of either anesthetic agent. This finding is similar to those of Bhardwaj et al. who performed jugular bulb oximetry and demonstrated that the use of desflurane was associated with hyperemia, that is, the mean values of jugular venous oxygen saturation (S\(\text{jV}0_2\)) were always on the higher side in the desflurane group as compared to propofol group in which the values were within the normal range at all times. However, this difference in the S\(\text{jV}0_2\) values among the two groups did not affect the intraoperative brain condition.\(^5\) Hence, that the changes in cerebral physiology associated with these agents may not necessarily translate into adverse brain conditions.

In another study, propofol and desflurane were compared for brain relaxation where burst suppression doses of these agents were used during cerebral aneurysm surgery. The authors found all patients to have Grade 1, that is, good brain relaxation when either of the agents was used.\(^4\) Our findings are similar to this study. Although their study used burst suppression doses of anesthetics while our study titrated the anesthetic agents to BIS, no difference in brain relaxation scores was found with the use of either propofol or desflurane. Furthermore, we have enrolled only good grade patients in our study where brain physiology is relatively preserved and this may lead to a comparable effect of anesthetics on brain relaxation.

Although different anesthetic agents have been variably studied using clinical outcome parameters in patients undergoing aneurysmal clipping, there is a dearth of information on the effect of the anesthetic agent on the biomarkers of neuronal injury. Ischemia caused by neuronal injury triggers inflammation in the neuronal tissue and hence the release of neuro-inflammation-related factors in the bloodstream. In our study, S\(\text{100B}\) and IL-6 were measured using ELISA. IL6 has shown the strongest univariate association to acute ischemic stroke. In many neurological disorders, S\(\text{100B}\) is used as a marker of glial death since it is a calcium-binding peptide.\(^11,15\) In our study, the preoperative, intraoperative, and postoperative values of S\(\text{100B}\) in the propofol group were analogous with the desflurane group. The same held for IL6 values when measured in both the groups, thereby indicating that the effect on the neurobiochemical microenvironment is uniform with the use of anesthetic agents that have a disparate effect on neurophysiology.

Our study has a few limitations. There was a plan to conduct a multivariate analysis of the study. However, there was no statistically significant difference in any outcome variable (e.g. GOS at 3 months, etc.) for the two groups and it could not be conducted. We enrolled only good grade (WFNS Grade I–II) aneurysmal SAH patients. Hence, the results of this study cannot be extrapolated to poor grade SAH patients who conceivably have raised ICP and may demonstrate variable clinical effects based on the anesthetics used. Further studies are required to study the effect of anesthetic drugs on outcomes in poor-grade aneurysmal SAH patients. Furthermore, anesthesiologists who managed the patient intraoperatively were not blinded to the agents used and this could be a source of bias. Finally, yet importantly, brain relaxation perceived is a subjective score. We did not use ICP monitoring during the procedure to correlate brain condition and ICP at that time.

To conclude, our study demonstrates that in patients with good grade SAH, the long-term outcome as measured by GOS at 3 months following discharge is comparable with the use of either propofol or desflurane. The intraoperative...
hemodynamics and brain condition, duration of hospital stay, mRS at discharge, mRS, and Barthel's Index at 3 months are comparable with the use of either agent. The effect of the two anesthetic agents on the biomarkers of brain injury is also similar.

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Declaration of patient consent
Institutional Review Board permission obtained for the study.

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Conflicts of interest
There are no conflicts of interest.

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