The effect of anaesthetic exposure in presurgical period on delayed cerebral ischaemia and neurological outcome in patients with aneurysmal subarachnoid haemorrhage undergoing clipping of aneurysm: A retrospective analysis

**INTRODUCTION**

Aneurysmal subarachnoid haemorrhage (aSAH) often leads to poor neurologic outcome. In general, one third of patients end up with significant disability.[1] Out of the survivors, only a third can resume the same functionality as before.[2] Out of the various complications mentioned, delayed cerebral ischaemia (DCI) remains the major contributor to the morbidity. DCI is defined as the onset of new global or focal neurologic deficit or radiologic evidence of a new stroke that is not attributable to another known cause.[2]
Ischaemic preconditioning is a phenomenon by which exposure to shorter periods of ischaemia makes an organ tolerant to subsequent periods of ischaemic insult. Innumerable trials have shown that a variety of preconditioning stimuli, including hypoxia, inhalation anaesthetics and many drugs, induce tolerance against subsequent cerebral ischaemic insults.\(^4,5\) Remote ischaemic preconditioning can also affect brain tolerance to ischaemia.\(^6\) In literature, anaesthetic induced preconditioning has been discussed in details. Usually preconditioning has two time courses: delayed preconditioning begins a day after the preconditioning stimulus and lasts for several days; immediate preconditioning requires treatment only minutes to an hour before the ischaemia.\(^7\) Anaesthetic induced preconditioning has been shown to be dependent on the activation of protein kinase-C (PKC) and the opening mitochondrial adenosine-triphosphate sensitive potassium channel (KATP channel).\(^8\) Previous studies have shown to prevent hippocampal neuronal injury in an in vitro model of cerebral ischaemia due to oxygen glucose derivation after exposure to isoflurane.\(^9\) Many such patients receive general anaesthesia (GA) for angiography in the preoperative period, which might have a cerebral preconditioning effect. To the best of our knowledge, no prior study has examined the effect of exposure to anaesthetic agents in the presurgical period and subsequent neurological outcome in aSAH patients after surgical clipping. Therefore, we hypothesised that presurgical exposure to general anaesthetics in aSAH patients may lead to good neurological outcome and decrease incidences of DCI and vasospasm. Our primary aim was to assess the effect of exposure to general anaesthesia during DSA in the preoperative period on neurologic outcome in terms of Glasgow outcome scale (GOS) in patients presenting with aSAH as compared to non-exposure to GA. Secondary objectives were to assess the effect of exposure to general anaesthesia during DSA in the preoperative period on DCI in terms of vasospasm and cerebral infarct on postoperative computed tomography (CT), tracheostomy and any event of death.

**METHODS**

After Institute Ethical Committee approval, we conducted a retrospective analysis of the data of patients with aSAH who were treated with aneurysmal clipping. All the data of the patients were kept confidential. Data were collected from electronic medical records, patient admission, operation theatre records, intensive care unit (ICU) records and discharge sheets. All patients with aSAH admitted to neurosurgical ICU between June 2014 and December 2017 were identified from a computerised patient registry. Demographic data as well as social and medical history were obtained from the medical records. Various parameters including post resuscitation Glasgow coma scale (GCS), World Federation of Neurosurgical Surgeons (WFNS) scores, American Society of Anaesthesiologists-physical status (ASA), any pre-existing motor weakness, anaemia, the anaesthetic technique (local anaesthesia versus general anaesthesia) during DSA, preoperative CT and DSA findings were recorded. Post operative complications such as radiographic vasospasm, cerebral infarct and DCI along with the duration of hospital stay were recorded. GOS at the time of hospital discharge was recorded. Any event of tracheostomy and death was also noted. We stratified the patients into two groups, namely, GA group and LA group based on the history of anaesthesia exposure during angiography. The GA group of patients received general anaesthesia (sevoflurane exposure), tracheal intubation/laryngeal mask airway (LMA) for angiography and the LA group of patients did not receive general anaesthesia, tracheal intubation/ laryngeal mask airway (LMA) for angiography.

Radiographically, vasospasm was defined by the evidence of vascular luminal narrowing on angiographic images as determined by the interventional neuroradiologist. We documented DCI based on the presence of new infarcts on CT or MRI developed along with occurrence of new focal neurological signs or decline in the level of consciousness after other aetiologies of the same (hydrocephalus, metabolic abnormality and seizure) had been excluded.\(^10\) GOS at hospital discharge was recorded from the electronic medical records. A GOS <3 was defined as a poor discharge outcome, whereas GOS 4, 5 were considered to be favourable outcomes at discharge.

All the statistical analyses were performed using STATA 12.0 (Stata Corp, College Station, TX). The R statistical software package (version 2.15.0) was used to calculate propensity scores. Clinical and demographic characteristics of patients were compared using Chi\(^2\) or t-tests as appropriate. Propensity score matching was done in order to generate a matched sample on the baseline demographic variables. Logistic regression analysis was done to examine the association of presurgical exposure to GA with neurological outcome at discharge, vasospasm and DCI. A \(P\) value <0.05 was considered significant.
RESULTS

From the database, we identified 278 patients of aSAH operated during the period of the study and out of which, 116 (41.7%) patients had received GA during DSA [Table 1]. Patients in the GA group were older as compared to the LA group (GA vs. LA: 51.8 ± 13.3 vs. 46.8 ± 12.1 years, \( P = 0.001 \)). Patients who received GA had a greater illness severity as measured by ASA (\( P = 0.001 \)) and lower mean GCS as compared to the patients who did not need general anaesthesia (GA vs. LA: 11.9 ± 3.13 vs. 14.3 ± 1.8, \( P = 0.001 \)). More patients in GA group were of higher WFNS score (\( P = 0.001 \)). In unmatched data, 69.0% patients in the GA group had bad outcome at discharge as assessed by GOS, whereas 33.3% had bad outcome in LA group (\( P = 0.001 \)). The incidences of vasospasm, DCI and mortality were higher in GA group [Table 2].

In a logistic regression model, the odds ratio (OR) for poor outcome at discharge in GA group as compared to local group was 4.4 (CI: 2.7–7.4), \( P = 0.001 \). The OR of vasospasm for GA group was 1.9 (CI: 1.1–3.1), \( P = 0.01 \). The OR of DCI for GA group was 1.5 (CI: 0.9–2.5), \( P = 0.10 \). We also observed higher odds of mortality in GA group with an OR of 3 (CI: 1.6–5.6), \( P = 0.001 \) [Table 3].

Propensity score matching yielded 114 (57 in each group) matched patients. After propensity matching, we found out the odds for poor outcome at discharge in GA group to that of local group to be 1.2 (OR = 1.2 [CI: 0.6–2.6], \( P = 0.57 \)). Similarly, the odds of vasospasm, DCI, tracheostomy and mortality were comparable in both the groups [Table 3 and Figure 1].

DISCUSSION

In this study, we conducted a retrospective analysis of the effect of a method of preconditioning, i.e., exposure to sevoflurane-based anaesthesia in the presurgical period, on outcome of the aSAH patients. The major finding from our analysis is that presurgical exposure to GA in DSA is not associated with good outcome at discharge. Similarly, the presurgical exposure to GA in DSA does not decrease the odds of vasospasm, DCI,

| Table 1: Demographic variables in the two groups |
|-----------------------------------------------|
| **Unmatched data**                            |
| GA (n=116)                             | LA (n=162)                             | \( P \) |
| Age                                         | 51.8±13.3*                             | 46.8±12.1  | 0.001 |
| Sex                                         |                                        |           |       |
| Male                                        | 48 (41.3)*                             | 81 (50)   | 0.15  |
| Female                                      | 68 (58.7)                              | 81 (50)   | 0.03  |
| Weight                                      | 59.3±11.1                              | 62.2±11.2 | 0.03  |
| Hypertension                                |                                        |           |       |
| Yes                                         | 53 (45.7)                              | 54 (33.3) | 0.3   |
| No                                          | 63 (54.31)                             | 108 (66.7) | 0.07  |
| ASA                                         |                                        |           |       |
| ASA 1                                       | 59 (50.9)                              | 111 (68.5)| 0.001 |
| ASA 2                                       | 46 (39.6)                              | 49 (30.3) | 0.001 |
| ASA 3                                       | 11 (9.5)                               | 2 (1.2)   | 0.03  |
| GCS                                         | 11.9±3.13                              | 14.3±1.8  | 0.001 |
| WFNS                                         |                                        |           |       |
| WFNS1                                       | 33 (28.4)                              | 135 (83.5)| 0.001 |
| WFNS2                                       | 21 (18.1)                              | 7 (4.3)   | 0.001 |
| WFNS3                                       | 15 (12.9)                              | 6 (3.7)   | 0.001 |
| WFNS4                                       | 41 (35.3)                              | 11 (6.8)  | 0.001 |
| WFNS5                                       | 6 (5.17)                               | 3 (1.8)   | 0.001 |
| Pre-existing motor weakness                  |                                        |           |       |
| Yes                                         | 49 (42.2)                              | 28 (17.8) | 0.001 |
| No                                          | 67 (57.7)                              | 134 (82.7)| 0.001 |
| Anaemia                                     |                                        |           |       |
| Yes                                         | 19 (16.4)                              | 18 (11.1) | 0.2   |
| No                                          | 97 (83.6)                              | 144 (88.9)| 0.2   |

*Data expressed as mean±SD, *Data expressed as number (percentage). GA – General anaesthesia, LA – Local anaesthesia, ASA – American Society of Anaesthesiologists, GCS – Glasgow Coma Scale, WFNS – World Federation of Neurologic Surgeons
tracheostomy and mortality. Logistic regression model of unmatched samples resulted higher odds of poor outcome in GA group. This can be explained on the basis of greater illness severity seen in the GA group.

Both the groups were different in their demographic and clinical profiles. The propensity score in nonrandomised studies equilibrates the baseline parameters of treatment and control groups by one-to-one or pair matching. During the course of the diseases, complications are more pronounced in the group with higher illness severity, which can affect the outcome; however, propensity score is generated considering the different pre-intervention baselines characteristics. This generated two groups with comparable baseline characteristics, which would serve as case and control for the analysis. Hence, we did a propensity-matched scoring to even out the baseline differences. In logistic regression model, after propensity matching, the odds of poor outcome were lower than the unmatched sample. We observed that in a matched group of patients, there is no difference in effect of exposure to GA or non-exposure to GA in terms of poor outcome.

In a retrospective study, the authors found that patients with pre-existing cerebrovascular disease (CVD) are less likely to develop radiographic vasospasm than patients without CVD. However, these endogenous protective mechanisms were not associated with reduced DCI or improved neurological outcome at discharge. From our study, we directly cannot prove the preconditioning effect of anaesthetic exposure.

Many other novel methods of preconditioning resulted in better neurological outcomes. In another study, authors induced a lower-limb remote ischaemia following aSAH and concluded this positively affects
the functional outcomes of patients with SAH.\[^{13}\] However, our study results are different, and could be attributable to lesser preconditioning effect of sevoflurane-based anaesthesia.

There are experimental reports on the neuroprotective effects of inhaled anaesthetics, for example, the reduction of cerebral metabolic rate of oxygen, as well as a postconditioning effect during the reperfusion phase in cases of acute ischaemic stroke.\[^{14}\] Indeed, Sivasankar \emph{et al.} reported better neurological outcome after endovascular treatment in GA if patients received inhalation anaesthesia compared with intravenous anaesthesia.\[^{15}\] In our analysis, because the GA group had a higher illness severity, a higher incidence of vasospasm, DCI and mortality; thus, one can certainly explain the poor odds of outcome in the GA group in the logistic regression model. In one study, the poor outcome of patients who underwent endovascular treatment of acute ischaemic stroke under conscious sedation was attributed to the modified treatment in cerebral ischaemia (mTICI) score, National Institute of Health Stroke Scale (NIHSS) score and history of previous TIA independently.\[^{16}\] Although the study was not conducted to compare the effect of GA and LA on the outcome, the findings suggest that in majority of the cases the outcome depends on the illness severity.

Many previous trials on stroke compared the effect of GA and LA during the procedure on outcome.\[^{17,18}\] The recently published AnStroke trial that compared the effect of GA with that of conscious sedation in endovascular treatment of acute ischaemic resulted in no difference in outcome at 3 months.\[^{18}\] Our study probes the preconditioning effect of exposure to GA in the presurgical period, which is conceptually different with respect to other such studies. Our study has various limitations. First of all, this study is a retrospective analysis of the data, which could have incurred sampling bias. Second, a small sample size after propensity matching might have been not adequate to infer a conclusion. A larger sample after matching in this regard is required to prove the beneficial or harmful effects of the GA. An added point could be the outcomes after aSAH are driven by a multitude of variables, not all of which might be ameliorated by ischaemic preconditioning. Therefore, the hypothesis would be best tested in a controlled, prospective study. We included WFNS as a baseline variable as it correlates better with outcome than Fisher grade which correlates more with risk of vasospasm.\[^{19}\] Also, WFNS is a more specific scoring method in predicting 28-day outcome in aSAH patients.\[^{20}\]

From this study, we can conclude that the exposure to GA in the presurgical period did not offer neuroprotection from the adverse effects as the odds of poor outcome were higher compare to non-exposure to GA group. However, in a matched analysis, the odds of poor outcome were much less than that of unmatched sample results, which is not significant, which may be due to the smaller sample size. Hence, future larger prospective studies must be conducted to gather enough evidence in this regard.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Washington CW, Zipfel GJ. Detection and monitoring of vasospasm and delayed cerebral ischemia: A review and assessment of the literature. Neurocrit Care 2011;15:312-7.
2. Passier PE, Visser-Meily JM, Rinkel GJ, Lindeman E, Post MW. Life satisfaction and return to work after aneurysmal subarachnoid hemorrhage. J Stroke Cerebrovasc Dis 2011;20:324-9.
3. Rowland MJ, Hadjippavou G, Kelly M, Westbrook J, Pattinson KT. Delayed cerebral ischaemia after subarachnoid haemorrhage: Looking beyond vasospasm. Br J Anaesth 2012;109:315-29.
4. Mengenthaler P, Dirnagl U. Protective conditioning of the brain: Expressway or roadblock? J Physiol 2011;589:4147-55.
5. Dirnagl U, Becker K, Meisel A. Preconditioning and tolerance against cerebral ischaemia: From experimental strategies to clinical use. Lancet Neurol 2009;8:398-412.
6. Hahn CD, Manlhiot C, Schmidt MR, Nielsen TT, Redington AN. Remote ischemic per-conditioning: A novel therapy for acute stroke? Stroke 2011;42:2960-2.
7. Kass IS, Cottrell JE, Abramowicz AE, Hou JY, Lei B. Brain metabolism, the pathophysiology of brain injury, and potential beneficial agents and techniques. In: Cottrell JE, Patel P editors. Cottrell and Patel’s Neuroanesthesia. 6th ed. Amsterdam: Elsevier; 2017. p. 1-18.
8. Clarkson AN. Anesthetic-mediated protection/preconditioning during cerebral ischemia. Life Sci 2007;80:1157-75.
9. Popovic R, Liniger R, Bickler PE. Anesthetics and mild hypothermia similarly prevent hippocampal neuron death in an in vitro model of cerebral ischemia. Anesthesiology 2000;92:1343-9.
10. Frontera JA, Fernandez A, Schmidt JM, Claassen J, Wartenberg KE, Badjatia N, \emph{et al.} Defining vasospasm after subarachnoid hemorrhage: What is the most clinically relevant definition? Stroke 2009;40:1963-8.
11. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011;46:399-424.
12. Kim YW, Zipfel GJ, Ogilvy CS, Pricola KL, Welch BG, Shakir N, \emph{et al.} Preconditioning effect on cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage. Neurosurgery 2014;74:351-8.
13. Laiwalla AN, Ooi YC, Liou R, Gonzalez NR. Matched cohort
analysis of the effects of limb remote ischemic conditioning in patients with aneurysmal subarachnoid hemorrhage. Transl Stroke Res 2016;7:42-8.

14. Hoffmann U, Sheng H, Ayata C, Warner DS. Anesthesia in experimental stroke research. Transl Stroke Res 2016;7:358-67.

15. Sivasankar C, Stiefel M, Miano TA, Kosiratna G, Yandrawatthanana S, Hurst R, et al. Anesthetic variation and potential impact of anesthetics used during endovascular management of acute ischemic stroke. J Neurointerv Surg 2016;8:1101-6.

16. Athiraman U, Abdallah AB, Kansagra A, Tempelhoff R. Endovascular treatment of acute ischemic stroke under conscious sedation: Predictors of poor outcomes. Indian J Anaesth 2018;62:951-7.

17. GALA Trial Collaborative Group, Lewis SC, Warlow CP, Bodenham AR, Colam B, et al. General anesthesia versus local anesthesia for carotid surgery (GALA): A multicentre, randomised controlled trial. Lancet 2008;372:2132-42.

18. Löwhagen Hendén P, Rentzos A, Karlsson JE, Rosengren L, Leiram B, Sundeman H, et al. General anesthesia versus conscious sedation for endovascular treatment of acute ischemic stroke: The AnStroke trial (Anesthesia During Stroke). Stroke 2017;48:1601-7.

19. van Donkelaar CE, Bakker NA, Voeger NJ, Uyttenboogaart M, Metzemaekers JD, Eshghi O, et al. Prediction of outcome after subarachnoid hemorrhage: Timing of clinical assessment. J Neurosurg 2017;126:52-9.

20. Mishra RK, Mahajan C, Kapoor I, Prabhakar H, Bithal PK. Comparison of full outline of UnResponsiveness (FOUR) score and the conventional scores in predicting outcome in aneurysmal subarachnoid haemorrhage patients. Indian J Anaesth 2019;63:295-9.