Original Article

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

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ABSTRACT

Background and Aims: Delayed cerebral ischaemia is one of the major contributors to morbidity in aneurysmal subarachnoid haemorrhage (aSAH). General anaesthesia (GA) in the presurgical period may have a preconditioning effect. The primary aim was to assess the effect of preoperative exposure to GA during digital subtraction angiography (DSA) on neurological outcome in patients presenting with aSAH. **Methods:** After Ethical Committee approval, we conducted a retrospective analysis of the data of patients with aSAH treated surgically. Patients, admitted to neurosurgical ICU (June 2014 and December 2017) with a computed tomography (CT) diagnosis of aSAH and underwent DSA, were included. DSA, done with or without exposure to a general anaesthetic, was classified to GA group and LA group, respectively. Propensity score matching was done on the baseline variables. Appropriate statistical methods were applied. **Results:** Of the 278 patients, 116 (41.7%) patients had received GA during DSA. Propensity matching yielded 114 (57 in each group) matched patients. In a logistic regression model, the odds ratio (OR) for poor outcome at discharge in GA group as compared to LA group was 4.4 (CI: 2.7–7.4), $P = 0.001$, whereas, in the matched data, the OR for poor outcome at discharge in GA group as compared to LA group was 1.2 (CI: 0.6–2.6), $P = 0.57$. **Conclusion:** The presurgical exposure to GA did not offer any neuroprotection and the odds of poor outcome were higher compare to non-exposure to GA group.

Key words: Anaesthesia general, cerebral infarction, Glasgow outcome scale, neuroprotection, subarachnoid haemorrhage

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.[3]

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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, the bad outcome in GA group was 54.4%, whereas that in LA group was 49.1% ($P = 0.5$). Similarly, incidences of vasospasm, DCI and mortality were comparable between these two groups [Table 2]. After 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			Matched data		
	GA (*n*=116)	LA (*n*=162)	*P*	GA (*n*=57)	LA (*n*=57)	*P*
Age	51.8±13.3*	46.8±12.1	0.001	49.3±12.1	50±12.4	0.76
Sex						
Male	48 (41.3)#	81 (50)	0.15	24 (42.1)	23 (40.3)	0.84
Female	68 (58.7)	81 (50)		33 (57.9)	34 (59.7)	
Weight	59.3±11.1	62.2±11.2	0.03	58.7±11.3	61.9±10.3	0.11
Hypertension						
Yes	53 (45.7)	54 (33.3)	0.03	18 (31.6)	27 (47.4)	0.08
No	63 (54.31)	108 (66.7)		39 (68.4)	30 (52.6)	
ASA						
ASA 1	59 (50.9)	111 (68.5)	0.001	38 (66.7)	29 (50.9)	0.04
ASA 2	46 (39.6)	49 (30.3)		15 (26.3)	27 (47.4)	
ASA 3	11 (9.5)	2 (1.2)		4 (7.0)	1 (1.7)	
GCS	11.9±3.13	14.3±1.8	0.001	13.1±2.9	13.2±2.8	0.79
WFNS						
WFNS1	33 (28.4)	135 (83.5)	0.001	30 (52.6)	33 (57.9)	0.4
WFNS2	21 (18.1)	7 (4.3)		10 (17.5)	4 (7)	
WFNS3	15 (12.9)	6 (3.7)		6 (10.5)	6 (10.5)	
WFNS4	41 (35.3)	11 (6.8)		7 (12.3)	11 (19.3)	
WFNS5	6 (5.17)	3 (1.8)		4 (7)	3 (5.3)	
Pre-existing motor weakness						
Yes	49 (42.2)	28 (17.8)	0.001	17 (29.9)	19 (33.3)	0.6
No	67 (57.7)	134 (82.7)		40 (70.2)	38 (66.7)	
Anaemia						
Yes	19 (16.4)	18 (11.1)	0.2	8 (14.0)	8 (14.0)	1.0
No	97 (83.6)	144 (88.9)		49 (86.0)	49 (86.0)	

*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

Table 2: The outcome in the two groups

	Unmatched data			Matched data		
	GA (*n*=116)	LA (*n*=162)	*P*	GA (*n*=57)	LA (*n*=57)	*P*
GOS						
Good	36 (31.0)*	108 (66.7)	0.001	26 (45.6)	29 (50.9)	0.5
Bad	80 (69.0)	54 (33.3)		31 (54.4)	28 (49.1)	
Tracheostomy						
No	47 (40.5)	127 (78.4)	0.001	31 (54.4)	39 (68.4)	0.12
Yes	69 (59.5)	35 (21.6)		26 (45.6)	18 (31.6)	
Vasospasm						
No	58 (50.0)	106 (65.4)	0.01	28 (49.1)	33 (57.9)	0.34
Yes	58 (50.0)	56 (34.6)		29 (50.9)	24 (42.1)	
Delayed cerebral ischaemia						
No	70 (60.3)	113 (69.8)	0.10	36 (63.1)	33 (57.9)	0.56
Yes	46 (39.7)	49 (30.2)		21 (36.9)	24 (42.1)	
Death						
Alive	83 (71.5)	143 (88.3)	0.001	45 (78.9)	47 (82.5)	0.63
Dead	33 (28.5)	19 (11.7)		12 (21.0)	10 (17.5)	

*Data are expressed as number (percentage). GA – General anaesthesia, LA – Local anaesthesia, GOS – Glasgow Outcome Scale at discharge

Table 3: Logistic regression analysis before and after propensity matching

Variables	LL	OR	UL	*P*
GOS: Poor outcome	2.7	4.4	7.4	0.001
Tracheostomy	3.1	5.3	9	0.001
Vasospasm	1.1	1.9	3.1	0.01
Delayed cerebral ischaemia	0.9	1.5	2.5	0.1
Died	1.6	3	5.6	0.001
Matched data				
GOS: Poor outcome	0.6	1.2	2.6	0.57
Tracheostomy	0.8	1.8	3.9	0.12
Vasospasm	0.7	1.4	2.9	0.34
Delayed cerebral ischaemia	0.4	0.8	1.7	0.56
Died	0.5	1.2	3.2	0.63

LL – Lower limit, OR – Odds ratio, UL – Upper limit, GOS – Glasgow Outcome Scale at discharge

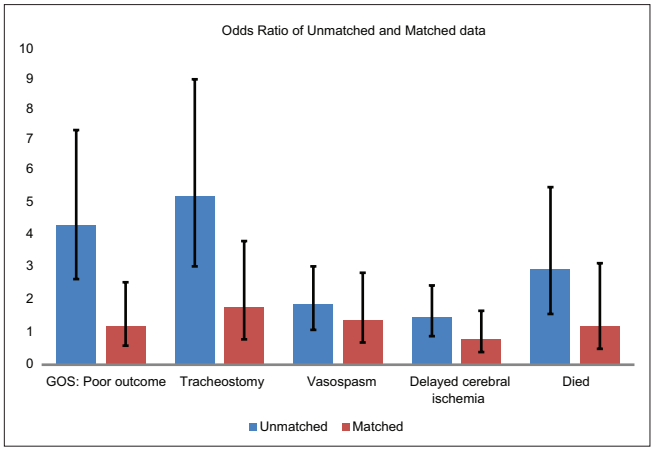

Figure 1: Odds ratio of unmatched and matched data for different outcomes

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.[11] 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.[12] 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 *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.

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Conflicts of interest
There are no conflicts of interest.

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