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Original Article

Assessment of impaired cerebral autoregulation and its correlation with neurological outcome in aneurysmal subarachnoid hemorrhage: A prospective and observational study

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ABSTRACT

Background: Cerebral autoregulation (CA) is crucial for the maintenance of cerebral homeostasis. It can be assessed by measuring transient hyperemic response ratio (THRR) using transcranial Doppler (TCD). We aimed at assessing the incidence of impaired CA (ICA) and its correlation with the neurological outcome in patients with aneurysmal subarachnoid hemorrhage (aSAH).

Methods: One hundred consecutive patients with aSAH scheduled for aneurysmal clipping were enrolled in this prospective and observational study. Preoperative and consecutive 5-day postoperative THRR measurements were taken. Primary objective of the study was to detect the incidence of ICA and its correlation with vasospasm (VS) postclipping, and neurological outcome at discharge and 1, 3, and 12 months was secondary objectives.

Results: ICA (THRR < 1.09) was observed in 69 patients preoperatively, 74 patients on the 1st and 2nd postoperative day, 76 patients on 3rd postoperative day, and 78 patients on 4th and 5th postoperative day. Significant VS was seen in 13.4% and 61.5% of patients with intact THRR and deranged THRR, respectively ($P < 0.000$). Out of 78 patients who had ICA, 42 patients (53.8%) at discharge, 60 patients (76.9%) at 1 month, 54 patients (69.2%) at 3 month, and 55 patients (70.5%) at 12 months had unfavorable neurological outcome significantly more than those with preserved CA.

Conclusion: Incidence of ICA assessed in aSAH patients varies from 69% to 78% in the perioperative period. The deranged CA was associated with significantly poor neurological outcome. Therefore, CA assessment using TCD-based THRR provides a simple, noninvasive bedside approach for predicting neurological outcome in aSAH.

Keywords: Cerebral autoregulation, Subarachnoid hemorrhage, Transcranial Doppler, Transient hyperemic response ratio

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is a neurosurgical emergency associated with a high rate of morbidity and mortality.[12] There is considerable long-term impairment following aSAH, resulting in a decline in the quality of life of survivors. The long-term neurological outcome is influenced not only by the initial severity of aSAH, but also by secondary brain injury caused by sequels of aSAH that follows ictal phase.

Cerebral autoregulation (CA) has been defined as the intrinsic ability of the cerebral vasculature to maintain a constant cerebral blood flow over a wide range of mean arterial blood pressure (MAP) (50–150 mmHg).[16,28] Disruption of CA early in the course of aSAH compromises cerebral perfusion and may cause ischemic injury.[7,15,24] Consequently, disturbed CA possibly has negative effect on the long- term functional outcome.

CA has two components – static and dynamic.[5] The static component is a gradual response to changes in MAP, whereas the dynamic component is a fast response to changes in pressure pulsation.[1,27] The dynamic component of CA in aSAH has received the majority of research attention because it employs noninvasive modalities, does not require vasoactive drug administration, allows for repeated measurements, and is less susceptible to changes in blood carbon dioxide levels. Transcranial Doppler (TCD) based transient hyperemic response test measures dynamic component of CA.[22] It evaluates changes in peak flow velocity (PFV) in intracerebral arteries after a brief compression of the ipsilateral common carotid artery.

We hypothesized that impaired CA (ICA) during initial period following aSAH can compromise cerebral perfusion which leads to poor neurological outcome even after successful surgical obliteration of aneurysm. Due to a dearth of published data on the occurrence of ICA in aSAH, we designed this prospective and observational study to determine the incidence of ICA in different grades of aSAH and to correlate ICA with neurological prognosis. The primary aim of the study was to detect the incidence of ICA by measurement of transient hyperemic response ratio (THRR) using TCD. Correlation of ICA with vasospasm (VS) postclipping and neurological outcome as measured by modified Rankin Scale (mRS) at discharge and Glasgow outcome scale extended (GOSE) at 1, 3, and 12 months was secondary outcomes of the study.

MATERIALS AND METHODS

A prospective and observational study was conducted in patients with aSAH admitted to a high-volume referral tertiary care institute. After obtaining the Institutes Ethics Committee approval (NK/3971/DM) and clinical trial registry India registration (CTRI/2018/02/011932), 100 consecutive aSAH patients planned for surgical clipping of aneurysm were enrolled in the study.

Patients aged >18 years and <65 years, having all grades of aneurysms according to Hunt and Hess (H&H), World Federation of Neurosurgical Society (WFNS), and Modified Fisher grades were included in the study. H&H grades (IV and V), WFNS grade (IV and V), and modified Fisher grade (III and IV) were considered as poor grade aSAH. Patients with carotid artery disease, ischemic stroke, hemodynamic instability, inadequate TCD window, angiographic VS on initial computed tomography angiography/digital subtraction angiography (DSA), and ruptured posterior circulation aneurysms were not included in the study. Patient or patient's next kin, if refuse to participate in the study, was also excluded from the study.

All patients underwent a detailed preanesthetic evaluation before surgery. A written informed consent was obtained from the patient or patient's next kin.

TCD protocol

In the preoperative period, bilateral carotid Doppler was performed to rule out carotid plaque or atheroma before enrolling the patients in the study to avoid the disruption and dislodgement of the plaque during THRR test. Elderly patients (defined by the World Health Organization as those being above 65 years of age) who have a higher prevalence of arterial atheromatous plaques were excluded from the study. In addition, the manipulation of the carotid in the neck appears to be an ostensibly harmless procedure, but it can occasionally lead to significant problems such as hypotension and bradycardia.[4] The TCD measurements were performed by a study investigator who was trained under a skilled ultra-sonographer and had performed more than 50 TCD measurements before starting this study. All TCD-derived cerebral blood velocities and THRR were measured in preoperative period and then once daily for 5 consecutive days in postoperative period, to assess incidence of ICA.

The TCD measurements were performed keeping patient in supine position. A 2 MHz frequency Doppler probe was used to insonate middle cerebral artery (MCA) at a depth of 30–60 mm, through temporal window using a TCD machine (RIMED Healthcare, Israel). The angle between the probe and skull was readjusted to obtain an optimal signal. The peak systolic flow velocity (FVs), end diastolic FV, and mean FV were assessed as cerebral blood flow velocities.

For measurement of THRR, the test was performed using Giller's maneuver with TCD probe in place on the side of the ruptured aneurysm while manually compressing the ipsilateral common carotid artery, with compression ratio of more than 50% of the baseline for 10 s.[11] With the release of compression, there was a hyperemic overshoot transiently. The MCA peak systolic flow velocity before compression, that is, baseline velocity (MCA FV1) was noted. After the release of compression, the first peak of the waveform corresponding to first cardiac cycle was ignored and next three cardiac cycles were equated, and the value was taken as MCA FV2 [Figure 1]. THRR was then calculated as the ratio of the MCA FV2/MCA FV1. A value of ≥1.09 was considered as intact CA, while values <1.09 were taken as ICA. The test was repeated 3 times at an interval of 2 min to eliminate false negative values due to mechanical error. If the peak flow velocity (PFV) returns to baseline after 10–20 s postrelease of carotid compression, it suggests as a marker of a good test quality.

The result of the tests measured for THRR was accepted if following criteria were met: (a) there was maximum and sudden decrease in MCA FV after compressing the carotid artery with no further decline in MCA FV, (b) heart rate and mean blood pressure remained stable during compression (i.e., within 10% of their respective precompression values), and (c) the reflected Doppler signal's power remained the same during the test.

Anesthesia protocol

In the intraoperative and postoperative period, a standard anesthesia technique and standard intensive care protocol, respectively, were followed in all the cases according to the institutional protocol. All surgeries were performed by a single experienced neurosurgeon in the early post-SAH phase (within first 3 days of arrival to the hospital post ictus). In the postoperative period, THRR measurements by TCD were performed in the patients for consecutive 5 postoperative days.

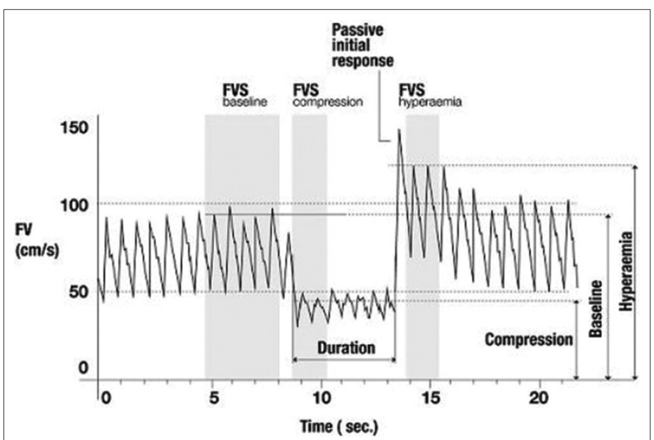

Figure 1: Measurement of transient hyperemic response ratio using transcranial Doppler by assessing hyperemic response after release of compression of carotid artery. FV: Flow velocity, FVS: Peak systolic flow velocity.

Incidence of cerebral VS was noted as per clinical, TCD, and angiographic criteria. Clinical criteria for cerebral VS were new onset neurological deterioration (hemiparesis, apraxia, neglect, aphasia, and hemianopia) or fall in Glasgow Coma Scale by >2 points and the duration of symptoms lasted for at least 1 h. An alert was sound, if there was increased cerebral blood FV on routine daily TCD evaluation of such patients. TCD confirmation of VS was done when mean cerebral blood FV in MCA was >120 cm/s and Lindegaard ratio was >3. Emergency angiographic study was performed within an hour of neurological deterioration.

At the time of discharge, mRS score was assessed and more than three score (mRS >3) was considered as unfavorable outcome. Later, all patients were followed up telephonically at 1, 3, and 12 months after discharge. Neurological outcome was evaluated using GOSE. Less than seven GOSE score was considered as unfavorable outcome. Correlation of ICA with neurological outcome as measured by mRS at discharge and GOSE at 1, 3, and 12 months was analyzed.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, version 21.0. Armonk, NY: IBM Corp). Normality of quantitative data was checked by Kolmogorov–Smirnov tests of normality. The continuous data were presented as mean ± standard deviation (SD) or median and inter quartile range, as appropriate. All measurable normally distributed data were expressed as mean and SD. Categorical and classified data were compared by χ^2 test or Fisher's exact test. Receiver operating characteristic (ROC) curve was drawn between ICA and neurological outcome to assess the sensitivity and specificity of THRR test with neurological outcome. $P < 0.05$ was regarded significant.

RESULTS

The study assessed a total of 105 patients, of whom five were excluded due to the inability to perform TCD insonation in three cases and the patient's family refusing to participate in two cases. As a result, 100 patients were included in the study and their data were analyzed [Figure 2].

All of the patients who participated in the study were separated into two groups: those who had preserved CA and those who had ICA. Demographic parameters and other baseline characteristics were comparable between these two groups [Table 1]. Autoregulation was found to be impaired (THRR < 1.09) in 69 patients preoperatively which increased to 74 patients on the 1st and 2nd postoperative day, which further increased to 76 patients on 3rd post-operative day, and 78 patients on 4th and 5th postoperative day [Figure 3].

Association of grading of aneurysms (H&H grading, WFNS grading, and Modified fisher grading) with the status of CA of the patients is shown in Table 2 and it was observed that greater number of poor grade aneurysms as per modified Fisher grading (Gr III and IV) had ICA ($P = 0.012$).

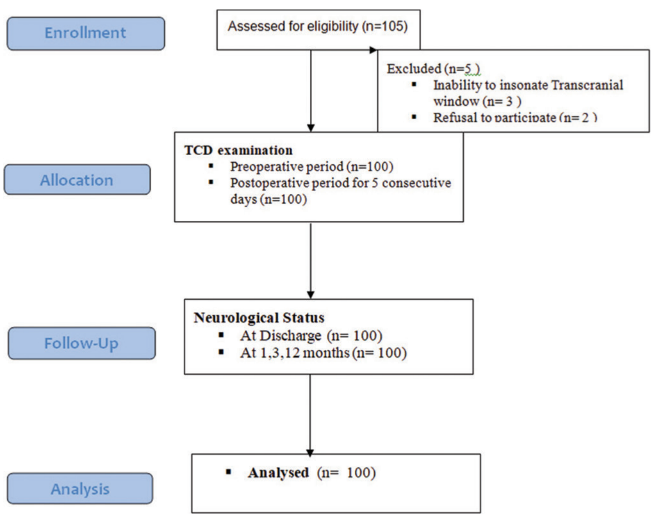

Figure 2: CONSORT diagram. n: Number, TCD: Transcranial doppler.

During postoperative period, 51% of patients had angiographically proven cerebral VS. Significant cerebral vasospasm was present in 3 patients (13.4%) out of 22 patients with intact THRR and 48 (61.5%) patients out of 78 patients with deranged THRR.

Among 78 patients of ICA, 42 (53.8%) patients had unfavorable outcomes at discharge (mRS $\geq$ 3). The difference between unfavorable and favorable outcomes in patients with ICA was statistically significant with $P = 0.020$ [Table 2]. A ROC curve was plotted between deranged THRR (ICA) and mRS at discharge [Figure 4]. Area under the curve for deranged THRR (ICA) was 0.678 ($P = 0.011$). These values had a sensitivity of 87.5% and specificity of 30.77% [Figure 4a].

During post discharge follow-up at 1 month, it was noted that the unfavorable outcome (GOSE < 7) was seen in 60 (76.9%) patients among ICA [Table 2]. A ROC curve between deranged THRR (ICA) and GOSE at 1 month after discharge showed area under the curve for deranged THRR (ICA) as 0.730 ($P = 0.001$). Values had a sensitivity of 88.24% and specificity of 43.75% [Figure 4b].

During post discharge follow-up at 3 months by GOSE showed that out of 78 patients of ICA, 54 (69.2%) patients

Table 1: Demographic parameters and baseline characteristics.

Parameters	Total (*n*=100)	Preserved CA (*n*=22)	Impaired CA (*n*=78)	*P*-value
Age in years	50 (41–58)	50 (39–57)	50 (42–60)	0.443
Gender				
Male	44 (44.0)	7 (31.8)	37 (47.4)	0.192
Female	56 (56.0)	15 (68.2)	41 (52.6)	
Hypertension {*n* (%)}	70 (70.0)	15 (68.2)	55 (70.5)	0.418
Diabetes mellitus {*n* (%)}	17 (17.0)	5 (22.7)	12 (15.4)	0.874
Obesity {*n* (%)}	24 (24.0)	5 (22.7)	19 (24.4)	0.499
History of smoking {*n* (%)}	38 (38.0)	7 (31.8)	31 (39.7)	0.228
History of alcohol intake {*n* (%)}	20 (20.0)	2 (9.1)	18 (23.1)	0.499
Chronic obstructive pulmonary disease {*n* (%)}	22 (22.0)	6 (27.3)	16 (20.5)	0.511
ASA status {*n* (%)}				
1	1 (1.0)	1 (4.5)	0 (0.0)	0.134
2	85 (85.0)	20 (90.9)	65 (83.3)	
3	11 (11.0)	1 (4.5)	10 (12.8)	
4	3 (3.0)	0 (0.0)	3 (3.8)	
H&H Grading {*n* (%)}				
Gr 1, 2 and 3	73 (73.0)	15 (68.2)	58 (74.4)	0.564
Gr 4 and 5	27 (27.0)	7 (31.8)	20 (25.6)	
WFNS Grading {*n* (%)}				
Gr 1, 2, and 3	84 (84.0)	20 (90.9)	64 (82.1)	0.512
Gr 4 and 5	16 (16.0)	2 (9.1)	14 (17.9)	
Modified Fisher grading {*n* (%)}				
Gr 0, 1, and 2	15 (15.0)	7 (31.8)	8 (10.3)	0.012*
Gr 3 and 4	85 (85.0)	15 (68.2)	70 (89.7)	
Postoperative cerebral vasospasm {*n* (%)}	51/100 (51)	3/22(13.6)	48/78 (61.5)	0.0001*

Values are presented as mean±standard deviation and number (*n*)/(percentage) or median (Interquartile range). **P*<0.05 is statistically significant.
ASA: American Society of Anesthesiologist, H&H: Hunt and Hess grade, WFNS: World Federation of Neurological Surgeons, CA: Cerebral autoregulation

had unfavorable outcome (GOSE ≤ 7) [Table 2]. A ROC curve for deranged THRR (ICA) with GOSE at 3 months after discharge showed area under the curve as 0.789 ($P = 0.000$). Values had a sensitivity of 91.53% and specificity of 41.46% [Figure 4c].

In 12 months post discharge follow-up, we found out of 78 patients with THRR <1.09, 55 (70.5%) patients had unfavorable outcome [Table 2]. A ROC curve for deranged THRR (ICA) with GOSE at 12 months after discharge showed area under the curve as 0.791 ($P = 0.000$).

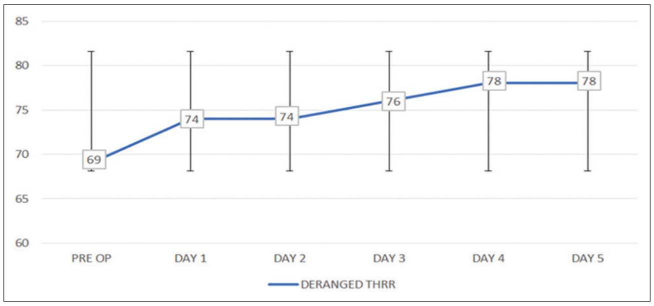

Figure 3: Line diagram showing trend of deranged transient hyperemic response ratio over the time period (preoperative to 5th postoperative period).

Values had a sensitivity of 89.74% and specificity of 63.64% [Figure 4d].

DISCUSSION

This prospective and observational study explored the incidence of deranged CA using THRR, in 100 consecutive aSAH patients who underwent surgical clipping following rupture of anterior cerebral circulation aneurysm. It was observed that 69% aSAH patients had ICA in post ictus (preoperative) period which increased to 78% on the postoperative day 5. Out of 78 patients, who had ICA, 53.8% ($n = 42$) at discharge, 76.9% ($n = 60$) at 1 month, 69.2% ($n = 54$) at 3 months, and 70.5% ($n = 55$) patients at 12 months had unfavorable neurological outcome, which was significantly higher than those with preserved CA.

CA is the elemental competency of cerebral arterial vessels to regulate their diameter, to uphold a proportionately consistent cerebral blood flow with shifts in cerebral perfusion pressure. Disturbance of CA over the early course of aSAH, conceivably increases the risk of delayed cerebral ischemia (DCI) and adversely impacts the long-term functional outcomes.[10,25] However, there is a paucity

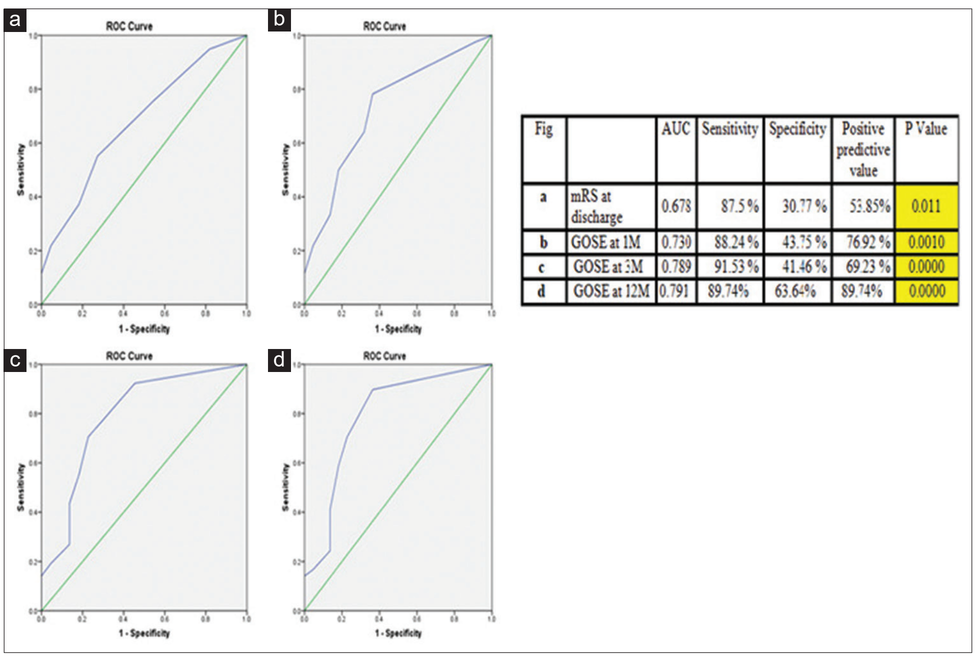

Fig		AUC	Sensitivity	Specificity	Positive predictive value	P Value
a	mRS at discharge	0.678	87.5 %	30.77 %	53.85%	0.011
b	GOSE at 1M	0.730	88.24 %	43.75 %	76.92 %	0.0010
c	GOSE at 3M	0.789	91.53 %	41.46 %	69.23 %	0.0000
d	GOSE at 12M	0.791	89.74%	63.64%	89.74%	0.0000

Figure 4: Receiver operating characteristic (ROC) curves analysis for unfavorable outcome in patients with impaired cerebral autoregulation (deranged transient hyperemic response ratio). (a) ROC at discharge, (b) ROC 1 month, (c) ROC at 3 months, and (d) ROC at 12 months. In Figure 4 the Green line is the Reference line (AUC=0.5) and the Blue line indicates ROC curve. Impaired Cerebral Autoregulation (assessed by deranged Transient Hyperemic Response Ratio) was associated with an unfavorable outcome. Area under curve (AUC) increased from discharge (Fig a) to maximum at follow up at 12 months (Fig d). Thus, the ROC curve shows that deranged transient hyperemic response ratio predicts unfavorable outcome with high sensitivity and specificity. Yellow indicates highly statistically significant. AUC: Area under the curve, mRS: modified rankin scale, GOSE: Glasgow outcome scale extended.

Table 2: Unfavorable neurological outcome and status of CA.

Time period	Unfavorable outcome preserved CA {*n* (%)}	Unfavorable outcome impaired CA {*n* (%)}	*P*-value
At discharge (by mRS)	6/22 (27.3)	42/78 (53.8)	0.011*
At 1 month (by GOSE)	8/22 (36.3)	60/78 (76.9)	0.001*
At 3 months (by GOSE)	5/22 (22.7)	54/78 (69.2)	0.000*
At 12 months (by GOSE)	5/22 (22.7)	55/78 (70.5)	0.000*

Continuous data expressed as number (percentage) and analyzed by Chi-square test. *$P \leq 0.05$ is considered statistically significant.
CA: Cerebral autoregulation, GOSE: Glasgow Outcome Scale Extended, mRS: modified Rankin Scale, *n*: Number

of literature describing incidence of ICA in patients with aSAH undergoing aneurysmal clipping. There are various methods to check integrity of CA such as measurement of THRR using TCD, brain tissue oxygen reactivity (ORx) and estimation of $PbtO_2$, regional cerebral oxygen saturation from near-infrared spectroscopy, and calculating cerebral oximetry index.[10,18]

The carotid compression test, also referred to as the THR test, was initially proposed by Giller as a clinical assessment tool for CA.[11] The underlying principle of this test is that the reflex vasodilation in the arterioles beyond the MCA should occur due to the decrease in MCA pressure caused by the compression of the common carotid artery, provided that autoregulation is functioning effectively. Consequently, the momentary release of compression would result in an increase in both MCA FV and cerebral blood flow. The results of TCD tests indicate a rise in FV, as illustrated in Figure 1. The absence of autoregulation results in the deficiency of the hyperemic response, as stated in reference 23. This test is characterized by its simplicity, noninvasiveness, and repeatability, thereby minimizing patient discomfort. This notion has garnered support from a multitude of inquiries conducted on both human and animal test subjects afflicted with conditions such as subarachnoid hemorrhage and traumatic brain injury.[6,14,15,23]

TCD can evaluate the status of CA by measuring the changes in peak flow velocity (PFV) in intracerebral arteries by briefly compressing the ipsilateral common carotid artery. According to Smielewski *et al.* well cited work, "the usual values of THRR measured in healthy individuals were between 1.105 and 1.29."[22] Hyperemic flow response above the threshold is labeled as "positive" (good autoregulation) and below that threshold is labeled as "negative" (impaired autoregulation).[27] Smielewski *et al.* also tested THRR in head-injured patients as a way to measure CA. They found that a THRR of 1.09 should be considered the lower limit of intact autoregulation even in patients with a traumatic brain injury.[23] The same THRR value was used in our study for evaluation of CA. In our study, it was observed that 69% of aneurysmal SAH patients had ICA in post ictus (preoperative) period while the incidence increased to 78% on 5th postoperative day. Rynkowski *et al.* examined CA by THRR within 72 h on 40 aSAH patients in a prospective and observational trial and observed ICA in 47.5% of patients.[21] We assessed CA in 100 cases of aSAH and evaluated it from preoperative period to 5th postoperative day.

Disturbance of CA over the early course of aneurysmal SAH is increasingly known to cause VS, cerebral infarction, and poor neurological outcome.[19,20,27] Various studies have focused on TCD as a tool for prediction of VS and it has been recommended as Class II level of evidence to monitor cerebral VS following aSAH.[5,17,26] In our study, 51% of patients developed VS. In deranged CA group, 61.5% of patients developed VS (48 out of 78 patients) while in intact autoregulation group, only 13.6% of patients had VS (only three out of 22 patients), ($P < 0.0001$). In a retrospective study, authors found that 83% of patients in the VS group had an abnormal transient hyperemic response ($P = 0.0406$).[2] Fontana *et al.* studied association of VS with dynamic autoregulation index (ARI) using leg cuff test for the first 8 days after aSAH.[8] They found that severity of deranged CA correlated significantly with the severity of VS ($P = 0.018$). Budohoski *et al.* reported autoregulation failure in aSAH patients who developed DCI and unfavorable outcome.[3] Another group of authors suggested that deranged CA exists before clinical or radiographic findings of cerebral VS.[9]

In the present study, all the patients were followed up at discharge using modified Rankin Score and at 1, 3, and 12 months after discharge using GOSE. We found a significant correlation between ICA and unfavorable GOSE at 1, 3, and 12 months. ($P = 0.001$, <0.001 and <0.001 respectively). Hence, deranged CA correlated well with unfavorable outcomes. Rynkowski *et al.* mentioned that patients in ICA group advanced to an unfavorable outcome compared to the preserved CA group (73.7% vs. 4.7%, $P = 0.0001$).[21] ICA group developed cerebral infarction more often as compared to preserved CA group (36.8% vs. 0%, $P = 0.003$, respectively). On multivariate analysis, ICA (odds ratio 5.15 95% confidence interval 1.43–51.99, $P = 0.033$) independently correlated with an unfavorable outcome. These findings were consistent with our study which also revealed that ICA is associated with worse neurological outcomes at discharge and till the time course of 1 year after discharge.

Fontana *et al*. studied the course of dynamic autoregulation by leg cuff test and dynamic ARI for initial 8 days following SAH and its association with angiographic VS and clinical outcome measured by mRS in 51 SAH patients prospectively.[8] The ARI was determined every-day using the thigh cuff test. The degree of cerebral VS was measured using the baseline DSA following the ictus and a follow-up DSA on day 8. The clinical outcome was measured using the mRS and GOSE, and the National Institute of Health Stroke Scale (NIHSS) at discharge from the intensive care unit. They found that ICA significantly correlated with unfavorable clinical outcome scores (mRS – P = 0.0021; GOSE – P = 0.0027; and NIHSS – P = 0.0091). The degree of CA impairment significantly correlated with the severity of VS in the MCA (P = 0.0184). Jaeger *et al*. tested CA using brain tissue ORx and $PbtO_2$.[13] A significant difference was found in patients with autoregulatory failure for unfavorable versus favorable outcome using GOS at 6 months (P = 0.001). Findings of various studies were consistent with our results in terms of worse neurological outcome in patients with ICA.

ICA may have a key role to play in the development of VS, DCI, cerebral infarction which in turn may result in poor neurological outcomes. Numerous pathological processes other than large vessel narrowing have been hypothesized. These include brain injury caused by global cerebral ischemia as a result of increased intracranial pressure secondary to initial bleeding, cortical spreading ischemia, microcirculatory VS, and cerebral micro thrombosis. However, it is not clear if these processes are discrete expressions of the same cerebrovascular failure or if they work as distinct entities.

Limitations

There were few limitations in our study. The study was limited to those patients who underwent clipping surgery. Although this gave homogeneity to the study population, patients undergoing coiling or managed conservatively could not be evaluated in the study. Postoperative rehabilitation programs and cognitive therapy which have vital influence on neurological outcome were not taken into account in the study while assessing postdischarge follow-up of the patient. A multi-centric study would have provided a more reliable validation of our findings with a larger sample size.

CONCLUSION

THRR measured by Transcranial Doppler is a simple, bedside, noninvasive, and repeatable test for assessment of CA. The incidence of ICA in patients with aneurysmal SAH evaluated by THRR using TCD varied from 69% to 78% in the perioperative period. The impaired autoregulation may predict unfavorable outcomes at discharge and poor neurological outcome at 1, 3, and 12 months. Further studies are needed to use THRR in different groups of patients with acute cerebral insult to focus on early recognition of ICA and target intensive therapies to improve overall neurological outcome.

List of drugs used

These standard drugs were used for induction and maintenance of anesthesia during surgery
1) Propofol
2) Fentanyl
3) Vecuronium
4) Phenytoin.

Ethics approval and consent to participate

Clearance to conduct the study was obtained from the Institute Ethics Committee in accordance with the Helsinki Declaration of 1975, as revised in 2000. Written informed consent was obtained from either patients or next of the kin all patients who participated in the study.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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