Original Article

Access this article online

Quick Response Code:

Website: www.neurologyindia.com

DOI: 10.4103/neurol-india.Neurol-India-D-25-00595

Effect of Pharmacological Neuroprotection During Surgical Clipping of Anterior Circulation Intracranial Aneurysm on Neurological Outcome—A Randomized Controlled Study

Kadarapura N. Gopalakrishna, Dhritiman Chakrabarti, Suparna Bharadwaj, Ramesh J. Venkatapura, Malla B. Rao[1], Shweta S. Naik, Nishanth Sadashiva[1], Dhananjaya Bhat[2]

Departments of Neuroanaesthesia and Neurocritical Care and [1]Neurosurgery, National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, Karnataka, [2]Department of Neurosurgery, Aster R V Hospital, Bengaluru, Karnataka, India

Address for correspondence:
Dr. Suparna Bharadwaj, Department of Neuroanaesthesia and Neurocritical Care, National Institute of Mental Health and Neuro Sciences (NIMHANS), Bengaluru - 560 029, Karnataka, India.
E-mail: acharya.suparna@gmail.com

Abstract:

Objective: Patients with intracranial aneurysms while undergoing neurosurgical clipping frequently require the use of temporary clip, and this involves the risk of cerebral ischemia. The usual approaches for prevention of such an adverse event include use of pharmacological neuroprotection before temporary clipping of the parent vessel to induce burst suppression of EEG, or detecting ischemia using somatosensory-evoked potential (SSEP) of the relevant arterial territorial distribution and taking corrective measures. We studied the effect of preemptive pharmacological neuroprotection on postoperative neurological deficit and outcome in patients undergoing anterior circulation intracranial aneurysm surgery.

Methods: Prospective, randomized, comparative study included adult patients requiring temporary parent vessel occlusion during surgical clipping of ruptured intracranial aneurysm of the anterior circulation. Patients were randomized to Group N (pharmacological neuroprotection) or Group I (non-pharmacological neuroprotection). Anesthesia induction, maintenance of anesthesia, and extubation were standardized in both the groups. Cerebral ischemia monitoring was conducted in both groups using SSEP. Group N ($n = 15$): received pharmacological neuroprotection using propofol bolus; Group I ($n = 15$): SSEP monitoring and alerting the surgeon to ischemia, and taking appropriate corrective measures.

Results: The demographic data were comparable between the two groups. There was no statistically significant difference in new onset neurological deficit within 24 hrs between the groups ($P = 0.64$). There was no significant difference in neurological outcome measured by the extended Glasgow Outcome Scale (GOSE), between the groups at three and six months.

Conclusion: This study shows no difference in short- or long-term neurological outcome with preemptive anesthetic neuroprotection during temporary arterial occlusion in anterior circulation intracranial aneurysm surgery. This pilot study was performed to estimate event rates and feasibility rather than to test efficacy.

Key Words:

Intracranial aneurysm, neurological outcome, neuroprotection, somatosensory-evoked potential, surgical clipping

Key Message:

- Preemptive pharmacological neuroprotection using propofol for anterior circulation aneurysm surgery did not significantly improve neurological outcomes.
- These findings suggest that routine use of pharmacological neuroprotection may not be essential and highlight the need for larger multicenter trials.

How to cite this article: Gopalakrishna KN, Chakrabarti D, Bharadwaj S, Venkatapura RJ, Rao MB, Naik SS, *et al*. Effect of Pharmacological Neuroprotection During Surgical Clipping of Anterior Circulation Intracranial Aneurysm on Neurological Outcome—A Randomized Controlled Study. Neurol India 2026;74:424-31.

Submitted: 22-Jul-2025 **Revised:** 16-Oct-2025
Accepted: 01-Jan-2026 **Published:** 06-May-2026

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 License (CC BY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

© 2026 Neurology India, Neurological Society of India | Published by Wolters Kluwer - Medknow

Intracranial aneurysms are treated via neurosurgical clipping or endovascular approaches. Intraoperative rupture is a major cause of morbidity and mortality in patients undergoing clipping, occurring in 8% to 19% of cases.[1,2] Surgical clipping often requires temporary arterial occlusion (TAO) of the parent vessel to aid visualization and dissection. While TAO helps minimize rupture risk, prolonged occlusion may impair distal cerebral perfusion, leading to ischemia and new-onset strokes.[3,4] Symptomatic strokes are seen in 10–12% of clipping procedures.[5,6]

To mitigate TAO-related ischemic injury, anesthetic boluses inducing EEG burst suppression are administered before vessel occlusion. These agents reduce cerebral activity, offering neuroprotection; however, they may also cause hypotension, potentially exacerbating cerebral ischemia. This contradiction raises questions about the actual benefit of pharmacological neuroprotection during aneurysm surgery.

Other strategies for reducing focal ischemic injury during TAO include intraoperative neurophysiological monitoring. Somatosensory-evoked potential (SSEP) monitoring helps detect cerebral ischemia in real time, allowing corrective actions like increasing blood pressure or altering clip positioning. The time from occlusion to recovery of baseline SSEP amplitude correlates with new postoperative deficits.[7] As SSEP reflects perfusion in the middle and anterior cerebral artery territories, it is particularly useful in anterior circulation aneurysm surgeries.

Despite theoretical support, concrete evidence for or against pharmacological neuroprotection remains lacking.[8,9] This study was designed to assess its role during surgical clipping of ruptured anterior circulation aneurysms in reducing new neurological deficits.

We hypothesized that preemptive pharmacological neuroprotection during surgical clipping of anterior circulation intracranial aneurysms decreased the incidence of TAO-related stroke in the early postoperative period.

Methods

Study design and patients

This prospective, single-center, randomized study was undertaken after the institute ethics committee approval (No. NIMHANS/IEC (BS and NS DIV.)/24th MEETING/2020) and was registered under Clinical Trial Registry of India (CTRI No: CTRI/2019/10/021496).

Primary objective: To evaluate the difference in new-onset neurological deficit within 24 hours postoperatively with or without pharmacological neuroprotection.

Secondary objective: To compare neurological outcomes between the groups using GCS at discharge and the extended Glasgow Outcome Scale (GOSE) at three and six months.[10]

This was an open-label randomized pilot study without blinding. Consecutive adult patients (18 to 65 years) undergoing surgical clipping of ruptured intracranial aneurysm of the anterior circulation were enrolled in the study. The patients with the previous history suggestive of stroke or coronary event, posterior circulation intracranial aneurysm, multiple intracranial aneurysm, and refusal to give consent were excluded. Based on computer-generated random numbers, patients were randomly assigned to either of two groups, Group N (pharmacological neuroprotection) or Group I (non-pharmacological neuroprotection).

Anesthesia induction, maintenance of anesthesia, and extubation were standardized in both the groups. Anesthesia was induced with fentanyl 2 microgram/Kg, Propofol 2 mg/Kg, lidocaine 1.5 mg/Kg, and muscle relaxation with vecuronium 0.1 mg/kg. After tracheal intubation, all patients were mechanically ventilated to maintain an end-tidal CO_2 of 30 to 32 mmHg. Intra-arterial blood pressure monitoring was used. Anesthesia maintenance with fentanyl and propofol was used. Propofol was administered via a target-controlled infusion system in the range from 3 to 5 microgram/ml (target effect site concentration) and was titrated to Entropy™ (GE Healthcare, Chicago, Illinois) value of 40 to 50. Temperature was monitored by a nasopharyngeal probe, and normothermia was maintained in both the groups. Mannitol 20% (0.5–1g/kg) was infused before dural opening. Intravenous fluid was titrated based on PPV (pulse pressure variation) to maintain less than 13%. All patients were monitored with SSEP during surgical clipping of the intracranial aneurysm. When the surgeon decided to place a temporary clip to the parent vessel of the aneurysm, separate interventions were conducted based on the randomization of the patients in either group.

Group N: Propofol bolus (higher target effect site concentration) used to achieve a burst suppression ratio (BSR) of more than 50% based on Entropy™ monitor before temporary clipping. Blood pressure was maintained 10 to 20% above the baseline with fluid and titrated doses of mephentermine injection (3 to 6 mg)/phenylephrine bolus (50 to 100 microgram) or infusion. A baseline SSEP was recorded after achieving burst suppression and immediately before temporary clipping.

Group I: Baseline SSEP recording was obtained before temporary clipping. Any significant changes in SSEP occurring after clip application suggesting cerebral ischemia, was informed to the surgeon. Simultaneously appropriate non-pharmacological measures, such as increasing the blood pressure or alerting the surgeon for removal/manipulation of clip, were taken. If SSEP decline persisted after 2 minutes of corrective measures, pharmacological neuroprotection with propofol was initiated.

SSEP is monitored using NIM-ECLIPSE™ neuromonitoring system (Medtronic Xomed, Inc, USA). Sterile subdermal needle electrodes were used for stimulation of the median and tibial nerves for the upper limb and lower limb SSEP, respectively. The electrical stimulus for SSEP was accomplished by a square-wave pulse with a duration of 0.1 to 0.3 ms, stimulation intensity ranged from 15 mA to 30 mA, and frequency of 3–5 Hz. The cork-screw electrodes were placed on the patient's scalp based on the international 10–20 system to record cortical-evoked potential and for EEG monitoring. Cortical-evoked potential response was recorded from C3′ (2 cms behind C3; stimulation of right median nerve), C4′ (2 cms behind C4; for stimulation of left median N), and Cz′ (2 cms behind Cz; for bilateral tibial nerve stimulation).

Alarming criteria: Significant SSEP changes were defined as either a 50% amplitude reduction or a 10% latency prolongation of the upper extremity SSEP N20-P25 complex or the lower extremity SSEP N37-P40 complex as compared with baseline.[11] The cerebral ischemic changes on SSEP, onset of ischemia changes, duration of ischemic changes, and time for improvement to baseline were noted. The decision to remove the temporary clip, irrespective of alarms, was based on operating neurosurgeon. As part of the institute policy, in uneventful temporary clipping scenarios, reperfusion breaks are provided after approximately 5 minutes. When multiple temporary clippings were used, a minimum of 5 minutes of perfusion period was maintained between the temporary clippings. After the aneurysm was clipped, mean arterial pressure was kept at 10 to 20% above the baseline. The SSEP monitoring was continued till dural closure. Any intraoperative or postoperative complications were noted. Based on the preoperative clinical status and intraoperative events, patients were planned for extubation or elective ventilation.

Outcomes

The primary outcome of this study was to find the difference in incidence of new postoperative neurological deficits within 24 hours with or without preemptive pharmacological neuroprotection during temporary clipping of anterior circulation intracranial aneurysm surgery. New deficits at 24 hours were determined by standardized clinical neurological examination. Postoperative imaging (CT) was performed when clinical deterioration occurred; routine imaging was not performed for all patients. The secondary outcome was to find a difference in neurological outcomes between the groups as measured by GCS at discharge, extended GOSE at three months and six months. Assessment of the primary outcome was limited to 24 hours following aneurysm clipping to capture immediate ischemic injury temporally related to intraoperative events and SSEP changes

Data collection

Data collected included demographic variables (age, sex, comorbidities, World federation of neurological societies (WFNS) grade, Fisher grade), duration since ictus, cerebral angiography for location of aneurysm and angiographic cerebral vasospasm, incidence of intraoperative hypotension, incidence of aneurysm rupture, temporary clipping time duration, number of occlusive episodes, onset and duration of SSEP-based cerebral ischemic changes, duration of burst suppression, postoperative extubation status, postoperative new neurological deficit within 24 hours, incidence and duration of cerebral vasospasm, delayed cerebral ischemia (DCI), duration of hospital stay, GCS at discharge, and telephone-based structured interview for the extended GOSE/mortality at three and six months.[10] DCI was defined as new clinical deterioration attributable to ischemia. Imaging was obtained when clinically indicated.

Statistical analysis

Data were collated offline in a Microsoft Excel 2007 spreadsheet and analyzed using R version 4.2.1.[12] Interval and ordinal scale variables are presented as median and interquartile ranges, while nominal data are presented as frequencies and percentages. Due to the small sample size, a nonparametric test (Mann–Whitney *U* test) was used for analyzing group differences for interval and ordinal scale data. Nominal data were analyzed using the Chi-square test or the Fisher's exact test as appropriate. $P < 0.05$ was taken as the level for statistical significance. Since this study is being presented on a pilot basis, sample size calculation has been presented for important outcome variables. Sample size was calculated for important outcome variables modeled using the difference of proportions for independent samples and was conducted using G-power software version 3.1.9.4. Sample size estimates provided were calculated aiming at 80% study power with an acceptable alpha error rate at 5%.

Results

The study was conducted from November 2020 to October 2022 at a tertiary care Neuroscience hospital, in southern India. The results represent analysis of the pilot study, conducted after data of 30 patients (15 patients per group) had been collected. Fifty-two patients were considered for eligibility. The flow of patients into the study is shown in Figure 1. Data of 30 patients were analyzed. Descriptive data and group comparison of demographic and baseline variables are shown in Table 1. There were no statistically significant differences between groups for primary and secondary outcomes [see Tables 1–3] Difference of intraoperative, postoperative, and follow-up variables between groups is shown in Table 2. Intraoperative aneurysm rupture occurred in four patients of Group N and two patients of Group I ($P = 0.64$). Ischemic changes in SSEP were seen in three patients in Group N and one patient of Group I ($P = 0.59$), all four patients had intra-operative rupture and longer temporary clipping duration (more than 12–15 minutes). Among the three patients in Group N who exhibited ischemic changes on SSEP, two showed reversal of these changes intraoperatively; however, one of them still developed a postoperative neurological deficit despite the reversal. One Group N patient had persistent intraoperative SSEP changes and subsequently developed a postoperative neurological deficit. One patient with ischemic changes on SSEP in Group I had reversal of ischemic changes without postoperative neurological deficit.

Incidence of delayed cerebral ischemia was lower in Group N ($P = 0.245$), but was not statistically significant.

In Group I, two patients developed new neurological deficits without significant intraoperative SSEP changes. In Group N, four patients developed postoperative deficits; two of these had intraoperative SSEP ischemic changes. In Group I, one of the two patients who experienced intraoperative aneurysm rupture developed a new neurological deficit. In Group N, three of the four patients with intraoperative rupture developed new deficits. Additionally, one patient in each group developed a new neurological deficit despite the absence of intraoperative rupture. Intraoperative ischemic changes diagnosed via SSEP amplitude reductions predicted postoperative neurological deficits with high specificity (91.7%) but poor sensitivity (33.3%). Five patients remained intubated postoperatively due to clinical instability/sedation; two patients had new neurological deficits. Effect size estimates for study outcome variables are shown in Table 3. Based on this effect size of the outcome (new neurological deficits), a new sample size of 302 for future studies could be calculated.

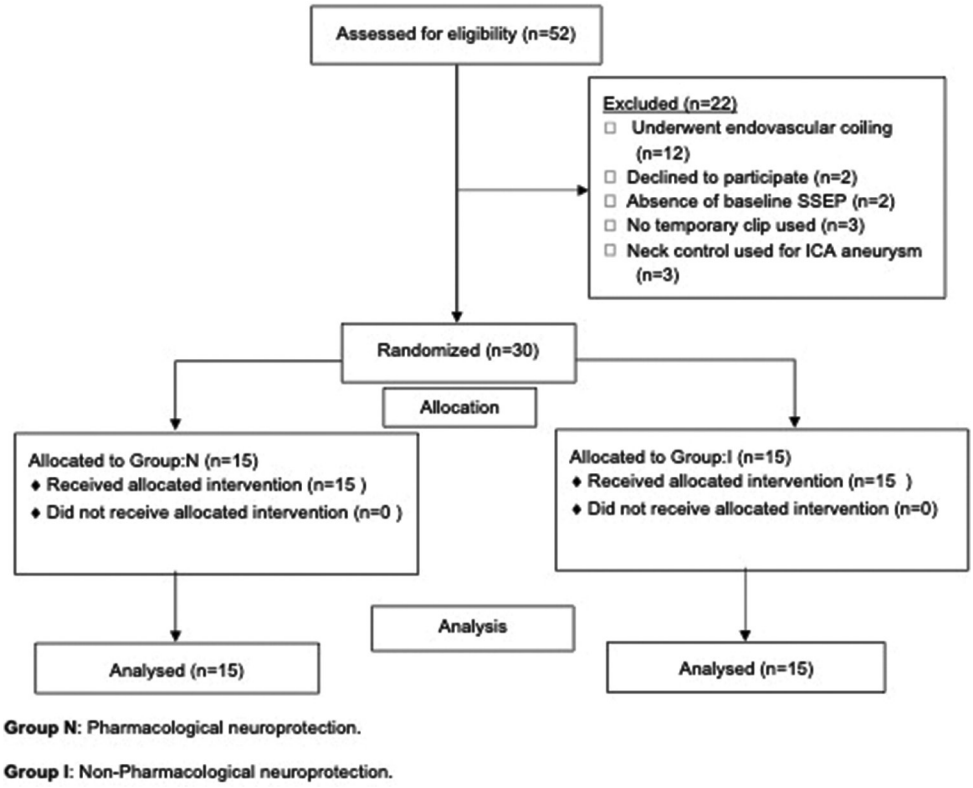

Figure 1: Flow diagram showing the flow of patients into the study

Table 1: Represents the distribution of baseline and demographic variables between the two study groups

Variable	Levels	Group N (*n*=15)	Group I (*n*=15)	*P*
Age (years)	-	47 (40–55)	45 (41–58)	1
Sex	Male	9 (60%)	3 (20%)	0.062
Comorbidities	DM	2 (13.33%)	0 (0%)	0.192
	HTN	5 (33.33%)	3 (20%)	
	None	8 (53.33%)	12 (80%)	
Aneurysm location	A-Com	10 (66.67%)	13 (86.67%)	0.131
	DACA	0 (0%)	1 (6.67%)	
	MCA	5 (33.33%)	1 (6.67%)	
WFNS grade	-	1 (1–1)	1 (1–1.5)	0.574
Duration since ictus (days)	-	4 (3–12)	5 (3–8.5)	0.85
Miller Fisher scores	-	3 (3–3)	3 (1–3)	0.193
Baseline GCS	-	15 (15–15)	15 (15–15)	0.976
Baseline HR (/min)	-	76 (66–88.5)	80 (77.5–84.5)	0.787
Baseline MAP (mm Hg)	-	93 (90–97)	97 (86.5–101.5)	0.533

Group N: Pharmacological neuroprotection. Group I: Non-pharmacological neuroprotection
DM—Diabetes mellites; HTN—Hypertension; A-Com—Anterior communicating; DACA—Distal anterior cerebral artery; MCA—Middle cerebral artery; WFNS—World federation of neurological societies; GCS—Glasgow coma scale
P<0.05 is the level for statistical significance

Discussion

This randomized controlled study evaluated the utility of anesthetic neuroprotection during temporary clipping in ruptured anterior circulation intracranial aneurysm surgery. Preemptive pharmacological neuroprotection did not result in statistically significant differences in immediate postoperative neurological deficits, delayed cerebral ischemia (DCI), in-hospital mortality, GCS at discharge, or GOSE scores at three and six months.

Postoperative neurological deficit with neuroprotection is reported at 15–26%.[4,5,9,13] In our study, new neurological deficits occurred in 26.6% with neuroprotection and 13.3% without. These early deficits may reflect intraoperative clipping-related variables. Given surgeries were performed 3–12 days post-ictus, some 24hour deficits could reflect evolving DCI. We attributed deficits to intraoperative events when temporally SSEP prolongation supported this, but residual confounding cannot be excluded. Sparse literature is available on clipping-related neurological deficits. One prior study reported approximately 16% incidence of 24-hour deficits with pharmacological neuroprotection.[13] Differences across studies stem from varying definitions of postoperative stroke—some include entire hospital stays, whether caused by clipping or delayed ischemia. Theoretically, neuroprotection improves ischemia tolerance by lowering neuronal oxygen demand. Yet ischemic SSEP changes occurred in three Group N patients (20%) and one in Group I (6.7%) ($P = 0.591$). All had clipping durations exceeding 12–15 minutes due to intraoperative rupture. Higher clip frequency and rupture rate likely influenced outcomes. Wicks *et al*.[14] reported 10% SSEP changes in ruptured aneurysms with neuroprotection. The excess ruptures in Group N prevented meaningful associations. While aneurysm rupture could be included in regression analysis, our small sample size and low event rate limited its utility. Hindman *et al*.'s[15] IHAST data analysis

Table 2: Displays distribution of intraoperative, postoperative, and follow-up variables between study groups

Variable	Levels	Group N (*n*=15)	Group I (*n*=15)	*P*
Intraoperative variables				
Intraoperative hypotension	Yes	5 (33.33%)	2 (13.33%)	0.388
Intraoperative vasopressor use	Yes	3 (20%)	2 (13.33%)	1
Intraoperative aneurysm rupture	Yes	4 (26.67%)	2 (13.33%)	0.648
Total temporary clip duration (minutes, 75 percentile interquartile range)	-	3.17 (1.69–8.49)	3.67 (1.33–6.75)	0.854
Number of temporary clipping episodes	-	2 (1.5–3)	1 (1–2)	0.047*
Maximum duration of any single clip (minutes)	-	4 (2–5.5)	2 (1–4)	0.156
Propofol neuroprotection dose	-	3 (3–4)	NA	NA
TCI (microgram/ml))				
Maximum burst suppression ratio	-	50 (30–59.5)	NA	NA
Duration of burst suppression (minutes)	-	20 (7.5–30)	NA	NA
Ischemia changes on SSEP	Yes	3 (20%)	1 (6.67%)	0.591
Onset of Ischemia after temporary clipping (minutes) #	-	10 (9.5–12.5)	15 (15–15)	0.637
Duration of Ischemia Changes (minutes) ##	-	7 (5.5–8.5)	5 (5–5)	1
Time for improvement to baseline (minutes) ###	-	7.5 (6.25–8.75)	1 (1–1)	0.667
Extubation	Yes	12 (80%)	13 (86.67%)	1
Postoperative variables				
GCS postoperative Day 1	-	15 (13–15)	15 (14–15)	0.323
New neurological deficits within 24 hours	Yes	4 (26.67%)	2 (13.33%)	0.648
Cerebral vasospasm	Yes	9 (60%)	7 (46.67%)	0.714
Delayed cerebral ischemia (DCI)	Yes	3 (20%)	7 (46.67%)	0.245
Intra-arterial nimodipine therapy (number of patients)	Yes	9 (60%)	7 (46.67%)	0.714
Intra-arterial nimodipine therapy (number of therapies)	-	2 (0–4)	0 (0–4.5)	0.774
Intravenous milrinone therapy	Yes	2 (13.33%)	5 (33.33%)	0.388
Length of hospital stay (days)	-	10 (6–11)	7 (5–11)	0.602
GCS at discharge	-	15 (15–15)	15 (13–15)	0.228
In-hospital mortality	Yes	1 (6.67%)	1 (6.67%)	1
Follow-up variables				
GOSE at three months (ordinal)	-	8 (6.5–8)	7 (4.25–7.75)	0.15
GOSE at six months (ordinal)	-	8 (7.5–8)	8 (4.5–8)	0.395
GOSE at three months (dichotomized)	Favorable	14 (93.33%)	10 (71.43%)	0.285
	Unfavorable	1 (6.67%)	4 (28.57%)	
GOSE at six months (dichotomized)	favorable	13 (86.67%)	10 (71.43%)	0.58
	Unfavorable	2 (13.33%)	4 (28.57%)	
All-cause mortality at three months	Yes	1 (6.67%)	1 (7.14%)	0.96
All-cause mortality at six months	Yes	2 (13.33%)	1 (7.14%)	0.58

Group N: Pharmacological neuroprotection. Group I: Non-pharmacological neuroprotection.
TCI—Target controlled infusion; SSEP—somatosensory-evoked potential; GCS—Glasgow coma scale;
GOSE—Extended Glasgow Outcome Scale;
* *P*<0.05 is the level for statistical significance. One patient was lost to follow up in Group I.
# Onset of ischemia measured from application of the first temporary clip to the first significant SSEP change.
Duration of ischemia=time from first significant SSEP decline to recovery of amplitude above alarm threshold or to intervention.
Time to improvement to baseline=time from intervention to restoration of baseline SSEP amplitude

showed no effect of supplemental neuroprotective drugs on 24-hour outcomes while accounting for clip duration and hypothermia.

DCI occurred in 46.6% of the non-neuroprotection group versus 20% with neuroprotection, though not statistically significant. Lavine *et al*.[5] reported infarction rates of 15.8% (intravenous

Table 3: Effect size for study outcome variables (Odds ratios were caalculated for Group N in reference to Group I

Outcome variables	OR (95% CL)	Sample size
New neurological deficits with in 24 hours	2.3 (0.27–30.02)	302
In-hospital mortality	1 (0.01–83.98)	NA
GOSE at three months (dichotomized)	0.19 (0–2.29)	104
GOSE at six months (dichotomized)	0.4 (0.03–3.44)	242
All-cause mortality at three months	1 (0.01–83.98)	NA
All-cause mortality at six months	2.1 (0.1–135.87)	690

Group N: Pharmacological neuroprotection
Group I: Non-pharmacological neuroprotection
GOSE—Extended Glasgow Outcome Scale

neuroprotection) and 45.5% (non-intravenous). Cerebral vasospasm showed no group trend, consistent with blood product-driven pathogenesis.[16,17] Mahajan *et al*.[9] found no difference in DCI or vasospasm using propofol for neuroprotection, though SSEP was not employed. Mishra *et al*.[18] found no vasospasm/DCI difference between general and local anesthesia during angiography. Neurological deficits associated with DCI in this study are followed up until discharge (7 to 10 days). However, other studies have studied DCI from 7 to 30 days.[9,15] Although not statistically significant, the lower DCI incidence in Group N (20% vs 47%) is a hypothesis-generating signal that warrants confirmation in larger trials.

Although propofol-induced burst suppression can reduce SSEP amplitudes, moderate burst suppression levels in our protocol preserved recordable SSEP signals. SSEP changes predicted neurological deficits with high specificity (91.7%) and low sensitivity (33.3%). These results align with existing data showing a sensitivity of 25–50% and a specificity of 84–95%.[14,19-21] A stable cortical SSEP during clipping suggests adequate cerebral perfusion.[22] However, deep perforator territory infarctions may occur without affecting cortical signals. Thus, subcortical ischemia is a limitation in SSEP. Still, SSEP offers real-time feedback on cortical perfusion, and amplitude/latency changes can reflect inadequate collateral flow—helping guide clip duration and technique.[13]

Hypotension is a common concern with neuroprotection. In our study, hypotension occurred in 13% (Group I) and 33% (Group N), lower than the 78% incidence reported by Hoff *et al*.,[23] where hypotension (ΔMAP ≥ 30%) correlated with poor outcomes. ASA guidelines recommend minimizing hypotension during aneurysm procedures.[24] We used target-controlled infusion (TCI) of propofol to reach a gradual burst suppression ratio of 50%, resulting in slower blood concentration rise and reduced hypotension risk compared to manual bolus. Our protocol also emphasized timely vasopressor use. This entropy-guided titration differs from bolus thiopentone/propofol protocols used in older studies and likely reduces abrupt hypotension; this methodological difference should be considered when comparing results.

Postoperative outcomes, such as hospital stay and GCS at discharge, were comparable between groups. Mahajan *et al*.[9] reported no differences due to neuroprotection. Each group had one in-hospital death. GOSE scores at three and six months were slightly higher in the neuroprotection group, though not statistically significant. This parallels the IHAST study that found no outcome benefit from supplemental neuroprotective drugs, such as thiopentone or etomidate, when dosing and timing were not standardized.[15] Their large sample allowed examination of interactions between clip duration, neuroprotective drugs, and hypothermia, while our study supports larger randomized trials for validation. At six months, one Group N patient died from unrelated causes. Lavine *et al*.[5] found no long-term outcome difference for MCA aneurysms with or without intravenous neuroprotection.

Limitations of this study: This randomized controlled study was conducted to fill the void in exploration of a crucial piece of clinical intervention, which still remains shrouded in controversy. Since the manuscript is presentation of a pilot data analysis of a single center and due to small sample size, the results of the study should be interpreted with caution. With that in mind, allowance needs to be provided for interpreting the results which trend toward statistical significance. The authors have noted paucity of literature which provide appropriate data required for calculation of sample size for future studies. Hence, the sample size estimates of important outcome variables have also been provided [Table 3]. Due to requirement of larger sample sizes and constraints on availability of funding, present study has been terminated at the pilot stage. Lack of blinding may have introduced observer bias in outcome assessment. Other limitations, are, only ruptured anterior circulation aneurysm cases are included in the study. In this study, only SSEP was used to monitor cerebral ischemia during temporary clipping. However, motor-evoked potential (MEP) may improve the accuracy and sensitivity of stroke prevention.[6,25,26] The combined utility of SSEP and MEP should minimize the risk of cerebral ischemia during surgical clipping of complex anterior circulation intracranial aneurysm. The direct cortical stimulation (DCS) MEP has advantage of detecting only focal cortical and subcortical cerebral ischemia,[27] but practical problem of placing strip electrodes for cortical stimulation and there is risk of subdural bleeding and brain injury.[28] Baseline imbalances (sex distribution, higher number/duration of temporary clips, and more intraoperative ruptures in Group N) may have influenced outcomes and limit causal inference; these imbalances should be addressed in larger randomized trials or adjusted analyses.

Conclusion

This study shows no difference in risk of focal ischemic brain injury with or without pharmacological neuroprotection during temporary arterial occlusion in patients undergoing anterior circulation intracranial aneurysm surgery. The pharmacological neuroprotection had no significant difference in the neurological outcome at three and six months. The results of the study are preliminary and hypothesis generating. The authors believe that conduct of multicenter randomized controlled trials with standardized neuroprotection protocols might yield useful results at larger sample sizes.

CRediT authorship contribution statement:

All authors contributed to the study conception and design. Kadarapura Nanjundaiah Gopalakrishna (KNG) contributed to research design, data collection, data interpretation, and manuscript writing. Dhritiman Chakrabarti (DC) contributed

to research design, data interpretation, statistical analysis, and manuscript writing. Suparna Bharadwaj (SB) contributed to research design, data collection, data interpretation, and manuscript writing. Ramesh J Venkatapura (RJV) contributed to research design, data interpretation, and manuscript writing. Malla Bhaskara Rao (MBR) contributed to research design and data interpretation. Shweta S Naik (SSN) contributed to data interpretation and manuscript writing. Nishanth Sadashiva (NS) contributed to research design and data interpretation. Dhananjaya Bhat (DB) contributed to the research design. All authors read and approved the final version of the manuscript.

Acknowledgments

Special thanks are due to Mr. Sanjib Mohanty, Mr. Manjunath Gowda, Mr. John Andrews, and Mr. Divakar for their technical support in conducting this study in the operation theatre.

Financial support and sponsorship

ISNACC research grant by the Indian Society of Neuroanaesthesiology and Critical Care.

Conflicts of interest

There are no conflicts of interest.

Details of previous presentation of the work

The preliminary data were presented (virtual) at the ISNACC 2022 conference on January 21st, 2022, Kolkata, India.

References

1. Fridriksson S, Säveland H, Jakobsson KE, Edner G, Zygmunt S, Brandt L, *et al*. Intraoperative complications in aneurysm surgery: A prospective national study. J Neurosurg 2002;96:515-22.
2. Leipzig TJ, Morgan J, Horner TG, Payner T, Redelman K, Johnson CS. Analysis of intraoperative rupture in the surgical treatment of 1694 saccular aneurysms. Neurosurgery 2005;56:455-68; discussion 455.
3. Molyneux AJ, Kerr RSC, Yu LM, Clarke M, Sneade M, Yarnold JA, *et al*. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: A randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. Lancet 2005;366:809-17.
4. Samson D, Batjer HH, Bowman G, Mootz L, Krippner WJ, Meyer YJ, *et al*. A clinical study of the parameters and effects of temporary arterial occlusion in the management of intracranial aneurysms. Neurosurgery 1994;34:22-8; discussion 28.
5. Lavine SD, Masri LS, Levy ML, Giannotta SL. Temporary occlusion of the middle cerebral artery in intracranial aneurysm surgery: Time limitation and advantage of brain protection. J Neurosurg 1997;87:817-24.
6. Schramm J, Koht A, Schmidt G, Pechstein U, Taniguchi M, Fahlbusch R. Surgical and electrophysiological observations during clipping of 134 aneurysms with evoked potential monitoring. Neurosurgery 1990;26:61-70.
7. Wang M, Li Z, Fan X, Tao X, Qi L, Ling M, *et al*. A prediction of postoperative neurological deficits following intracranial aneurysm surgery using somatosensory evoked potential deterioration duration. Neurosurg Rev 2020;43:293-9.
8. Rhoney DH, Parker D Jr. Use of sedative and analgesic agents in neurotrauma patients: Effects on cerebral physiology. Neurol Res 2001;23:237-59.
9. Mahajan C, Chouhan RS, Rath GP, Dash HH, Suri A, Chandra PS, *et al*. Effect of intraoperative brain protection with propofol on postoperative cognition in patients undergoing temporary clipping during intracranial aneurysm surgery. Neurol India 2014;62:262-8.
10. Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow outcome scale and the extended Glasgow outcome scale: Guidelines for their use. J Neurotrauma 1998;15:573-85.
11. Nwachuku EL, Balzer JR, Yabes JG, Habeych ME, Crammond DJ, Thirumala PD. Diagnostic value of somatosensory evoked potential changes during carotid endarterectomy: A systematic review and meta-analysis. JAMA Neurol 2015;72:73-80.
12. R Core Team. R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2018. https://www.R-project.org/. [Last accessed on 2019 Mar 24].
13. Holland NR. Subcortical strokes from intracranial aneurysm surgery: Implications for intraoperative neuromonitoring. J Clin Neurophysiol 1998;15:439-46.
14. Wicks RT, Pradilla G, Raza SM, Hadelsberg U, Coon AL, Huang J, *et al*. Impact of changes in intraoperative somatosensory evoked potentials on stroke rates after clipping of intracranial aneurysms. Neurosurgery 2012;70:1114-24; discussion 1124.
15. Hindman BJ, Bayman EO, Pfisterer WK, Torner JC, Todd MM. No association between intraoperative hypothermia or supplemental protective drug and neurologic outcomes in patients undergoing temporary clipping during cerebral aneurysm surgery: Findings from the Intraoperative Hypothermia for Aneurysm Surgery Trial. Anesthesiology 2010;112:86-101.
16. Jones J, Sayre J, Chang R, Tian J, Szeder V, Gonzalez N, *et al*. Cerebral vasospasm patterns following aneurysmal subarachnoid hemorrhage: An angiographic study comparing coils with clips. J Neurointerv Surg 2015;7:803-7.
17. Kolias AG, Sen J, Belli A. Pathogenesis of cerebral vasospasm following aneurysmal subarachnoid hemorrhage: Putative mechanisms and novel approaches. J Neurosci Res 2009;87:1-11.
18. Mishra RK, Pandia MP, Kumar S, Singh GP, Kalaivani M. 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. Indian J Anaesth 2020;64:495-500.
19. Kashkoush AI, Nguyen C, Balzer J, Habeych M, Crammond DJ, Thirumala PD. Diagnostic accuracy of somatosensory evoked potentials during intracranial aneurysm clipping for perioperative stroke. J Clin Monit Comput 2020;34:811-9.
20. Kashkoush AI, Jankowitz BT, Gardner P, Friedlander RM, Chang YF, Crammond DJ, *et al*. Somatosensory evoked potentials during temporary arterial occlusion for intracranial aneurysm surgery: Predictive value for perioperative stroke. World Neurosurg 2017;104:442-51.
21. Zhu F, Chui J, Herrick I, Martin J. Intraoperative evoked potential monitoring for detecting cerebral injury during adult aneurysm clipping surgery: A systematic review and meta-analysis of diagnostic test accuracy. BMJ Open 2019;9:e022810.
22. Palatinsky EDA, McDonald H, Whittingham T, Selman W. SSEP and BAER monitoring of temporary clip application and induced hypotension during cerebrovascular surgery. In: VC LCT, editor. Intraoperative Monitoring Techniques in Neurosurgery. New York, NY: McGraw-Hill; 1994. p. 61-71.
23. Hoff RG, GW Vand, Mettes S, Verweij BH, Algra A, Rinkel GJ, *et al*. Hypotension in anaesthetized patients during aneurysm clipping: Not as bad as expected? Acta Anaesthesiol Scand 2008;52:1006-11.
24. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, *et al*. Guidelines for the management of aneurysmal subarachnoid hemorrhage: A guideline for healthcare professionals from the American Heart Association/American Stroke

Association. Stroke 2012;43:1711-37.
25. Miró Lladó J, López-Ojeda P, Pedro J, Marnov A, Contreras L, Pariente L, *et al*. Evaluation of multimodal intraoperative neurophysiologic monitoring during supratentorial aneurysm surgery: A comparative study. Neurosurg Rev 2022;45:2161-73.
26. Staarmann B, O'Neal K, Magner M, Zuccarello M. Sensitivity and specificity of intraoperative neuromonitoring for identifying safety and duration of temporary aneurysm clipping based on vascular territory, a multimodal strategy. World Neurosurg 2017;100:522-30.
27. Doron O, Silverstein JW, Likowski D, Kohut K, Ellis JA. Temporary vessel occlusion in cerebral aneurysm surgery guided by direct cortical motor evoked potentials. Acta Neurochir (Wien) 2022;164:1255-63.
28. Guo L, Gelb AW. The use of motor evoked potential monitoring during cerebral aneurysm surgery to predict pure motor deficits due to subcortical ischemia. Clin Neurophysiol 2011;122:648-55.