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Evaluation of markers of cerebral oxygenation and metabolism in patients undergoing clipping of cerebral aneurysm under total intravenous anesthesia versus inhalational anesthesia: A prospective randomized trial (COM-IVIN trial)

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Abstract:

INTRODUCTION: Anesthetic goals in patients undergoing clipping of cerebral aneurysm include maintenance of cerebral blood flow, oxygenation, and metabolism to avoid cerebral ischemia and maintenance of hemodynamic stability. We intend to study the influence of anesthetic agents on the outcome of aneurysmal subarachnoid hemorrhage (SAH).

MATERIALS AND METHODS: This is a prospective, randomized, parallel, single-center pilot trial approved by the Institutional Ethics Committee and is prospectively registered with the Clinical Trial Registry of India. Patients with aneurysmal SAH (aSAH) admitted to our institution for surgical clipping, fulfilling the trial inclusion criteria, will be randomized in a 1:1 allocation ratio utilizing a computerized random allocation sequence to receive either total intravenous anesthesia (n = 25) or inhalational anesthesia (n = 25). Our primary objective is to study the effects of these anesthetic techniques on cerebral oxygenation and metabolism in patients with aSAH. Our secondary objective is to evaluate the impact of these anesthetic techniques on the incidence of delayed cerebral ischemia and long-term patient outcomes in patients with aSAH. The Modified Rankin Score and Glasgow Outcome Scale (GOS) at discharge and 3 months following hospital discharge will be evaluated. An observer blinded to the study intervention will assess the outcome measures.

DISCUSSION: This study will provide more insight as to which is the ideal anesthetic agent that offers a better neurophysiological profile regarding intraoperative cerebral oxygenation and metabolism, thereby contributing to better postoperative outcomes in aSAH patients.

Keywords:

Delayed cerebral ischemia, jugular venous oxygen saturation, lactate oxygen index, propofol, sevoflurane

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a catastrophic neurological event associated with significant morbidity and mortality that requires definitive treatment by neurosurgical clipping or endovascular coiling after initial stabilization. There are

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limited data on the influence of anesthetic agents on the long-term outcome of aSAH. The anesthetic goals in patients undergoing surgical clipping of cerebral aneurysm include maintaining cerebral blood flow, oxygenation, and metabolism to protect the injured brain and maintain hemodynamic stability.[1] Although inhalational and intravenous (IV) anesthetics have varied pharmacodynamic and pharmacokinetic properties, what is noteworthy is the difference in neurophysiological profile. In a normal brain, propofol does not affect cerebral autoregulation significantly as it maintains the flow-metabolism coupling between cerebral metabolic rate and cerebral blood flow.[1,2] However, inhaled anesthetics such as sevoflurane do not maintain the flow-metabolism coupling wherein higher doses result in increased cerebral blood flow despite reducing cerebral metabolic rate.[2,3] Currently, there is inadequate evidence for establishing the superiority of a particular anesthetic approach for clipping cerebral aneurysms. Both these agents are used in the anesthetic management of clipping cerebral aneurysms. Moreover, there are lacunae in research on their effects on cerebral metabolism and oxygenation in patients with aSAH. We hypothesize that total IV anesthesia (TIVA) with propofol may provide a better cerebral oxygenation and metabolism profile than inhalational anesthesia (INHA) with sevoflurane in patients undergoing clipping of cerebral aneurysms.

Our study objectives are as follows

Primary objective

The primary objective of this study is to study and compare the effects of propofol-based TIVA and sevoflurane-based INHA on cerebral oxygenation and metabolism in patients undergoing clipping of cerebral aneurysm under general anesthesia.

Secondary objectives

1. To compare the incidence of delayed cerebral ischemia (DCI) between the two groups
2. To compare the neurological outcome at discharge and at 3 months postdischarge from the hospital between both groups.

Materials and Methods

Study design

This is a prospective, randomized, parallel, single-center pilot trial to evaluate the markers of cerebral oxygenation and metabolism in patients undergoing clipping of cerebral aneurysm under propofol-based TIVA and sevoflurane-based INHA. This study will be conducted at Sree Chitra Tirunal Institute for Medical Sciences and Technology, which is a university-level hospital under the Government of India. It is a high-volume, tertiary-level referral center for neurological and neurosurgical patients, including aSAH from the southern states of India. This study is approved by the Institutional Ethics Committee (IEC) (SCT/IEC/1970/NOVEMBER/2022) and prospectively registered with the Clinical Trial Registry of India (CTRI) (CTRI/2023/06/053493).

Participants/sample size calculation

We plan to conduct a pilot study with a sample size of 50, with an equal number of participants in each arm, i.e., 25 in the propofol-based TIVA group and 25 in the sevoflurane-based INHA group.

Inclusion criteria

1. American Society of Anesthesiologists (ASA) Class I–IV (class IV due to subarachnoid hemorrhage [SAH])
2. Both gender
3. Age 18–65 years, undergoing clipping of cerebral aneurysm in the neurosurgery operation theater
4. Consent by patient or closest of kin.

Exclusion criteria

1. ASA Class III, IV, and V
2. Age <18 years, >65 years
3. Severe cardiovascular, renal, hepatic, or endocrine disease
4. Pregnancy, postpartum, and lactating females
5. Drug allergy to propofol or fentanyl
6. Refusal of consent by the patient or closest of kin
7. Patients who are intubated and on mechanical ventilation
8. Emergency surgery.

Informed consent

This will be drafted in English and regional language, and consent will be obtained from the patient or the patient's legal representative.

Proposed study duration

30 months after IEC approval and trial registration.

Methodology

The patients will be screened for recruitment as per the inclusion and exclusion criteria. After obtaining informed consent, the patient will be recruited for the study. Eligible patients will be randomized to receive either propofol-based TIVA (n = 25) or sevoflurane-based INHA (n = 25) using a computerized random allocation sequence in a 1:1 allocation ratio by an independent investigator not involved with the conduct of the study conduct or data interpretation. The anesthetist involved in the perioperative management will be blinded to the study outcomes. The data collector and the patient will be blinded to the type of anesthesia provided. The study methodology is represented in Figure 1.

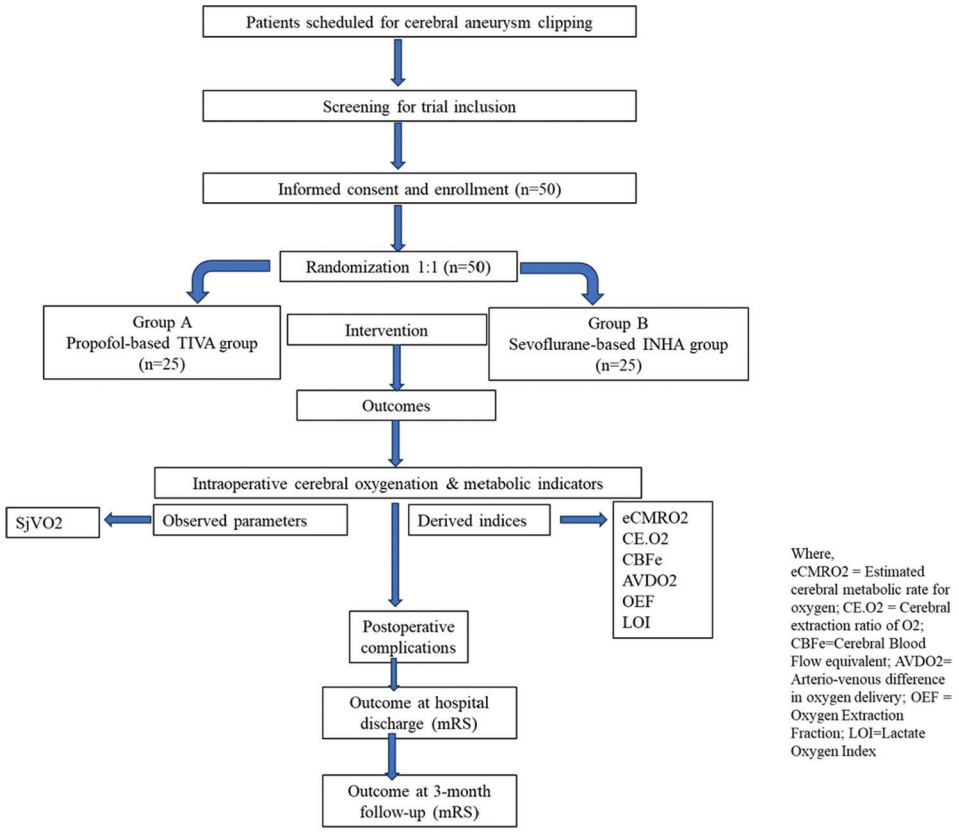

Figure 1: Schematic representation of the study methodology

Anesthesia protocol

Preanesthesia induction phase

i. Patients will be allocated to the TIVA or INHA group using a sealed opaque envelope technique by the attending anesthesiologist not involved with the study data collection or analysis
ii. ASA standard monitoring consisting of electrocardiogram, pulse oximeter (SpO_2), and noninvasive blood pressure monitoring will be initiated. In addition, a bi-spectral index (BIS) monitor will be placed to assess the depth of anesthesia (DoA).

Anesthesia induction phase

Group A: Propofol-based total intravenous anesthesia group

After preoxygenation with 100% oxygen for 3–5 min, anesthesia will be induced as per the institutional protocol using IV propofol 2–3 mg/kg titrated to a BIS of 40–60, along with fentanyl 2–3 μg/kg. After confirmation of bag and mask ventilation, injection vecuronium 0.08–0.12 mg/kg will be administered.

Group B: Sevoflurane-based inhalational group

After preoxygenation with 100% oxygen for 3–5 min, anesthesia will be induced as per the institutional protocol using IV thiopentone sodium 5–7 mg/kg titrated to BIS of 40–60 and 2–3 μg/kg of fentanyl. Injection vecuronium 0.08–0.1 mg/kg will be administered after confirmation of bag and mask ventilation.

Following endotracheal intubation, the volume control mode of ventilation will be used for ventilation using oxygen: air at a 1:1 ratio. Ventilatory parameters will be titrated to target an end-tidal carbon dioxide ($EtCO_2$) of 30–35 mmHg and arterial partial pressure of carbon dioxide ($PaCO_2$) of 35–40 mmHg.

Maintenance of anesthesia

Group A: Propofol-based total intravenous anesthesia group

Anesthesia will be maintained with TIVA using propofol 100–200 μg/kg/min along with fentanyl 1–3 μg/kg/h and atracurium 0.3–0.6 mg/kg/h. Propofol will be titrated to maintain a BIS of 40–60. We aim to target a burst suppression ratio (BSR) of 50% during the phase of temporary clipping.

Group B: Sevoflurane-based inhalational group

Anesthesia will be maintained with sevoflurane targeting a minimum alveolar concentration of 0.8–1 and a BIS of 40–60 till the craniotomy phase. In addition, IV fentanyl 1–3 μg/kg/h and atracurium 0.3–0.6 mg/kg/h infusion will be administered for maintenance. We aim to target a BSR of 50% during the phase of temporary clipping.

In both groups, regional anesthesia will be administered with bilateral scalp block using 2% lignocaine (3 mg/kg) and 0.5% bupivacaine (2.5–3 mg/kg). Ultrasound (USG)-guided right subclavian venous access will be obtained. Invasive arterial access will be obtained for monitoring invasive blood pressure monitoring and arterial blood gas (ABG) sampling. Vascular USG is utilized to identify the dominant jugular vein, and jugular catheter placement is done under USG guidance to monitor the jugular venous oximetry ($SjvO_2$). The tip of the catheter is positioned at the level of the jugular bulb, which will be confirmed with fluoroscopy.

Data collection

In addition to patient demographic and baseline clinical data, the following information will be collected. All the following parameters will be monitored continuously and recorded at five time points.

Time points for data collection

1. Immediately after cannulation (baseline) (T0)
2. After opening the dura (T1)
3. After temporary clipping if applicable (Tt)

Additional samples will be obtained in case of multiple temporary clip applications:

4. After permanent clipping (T2)
5. 6 h postextubation in neurosurgery intensive care unit (ICU) (T3)
6. Every 6th h if sedated and mechanically ventilated for 24 h (T4).

Hemodynamic and biochemical data collection

Observed parameters

a. Baseline heart rate, SpO_2, systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse pressure variation, and $EtCO_2$
b. Brain edema score will be recorded during the time of dural opening
    1. Grade1: Brain parenchyma is bulging above the level of craniotomy
    2. Grade 2: Brain parenchyma at the level of craniotomy
    3. Grade 3: Brain parenchyma is below the level of craniotomy
c. $PaCO_2$ obtained from ABG sampling from T0–T4
d. $SjVO_2$ values from jugular venous blood sampling from T0–T4.

Derived parameters

The derived parameters were calculated from the observed parameters at each time point from T0–T4 [Table 1].

Other relevant intraoperative data

Duration of surgery, urine output, volume of blood loss, blood transfusion if any, total intraoperative consumption of opioids, and recovery time.

Data regarding postoperative complications

Delayed recovery, vasospasm, DCI, prolonged ventilation, and postoperative tracheostomy.

Outcome data

Number of days in ICU, no of days in hospital, and Modified Rankin Scale (mRS) and Glasgow Outcome Scale (GOS) at discharge will be recorded. Follow-up of all patients will be done at 3 months using mRS and GOS.

Expected outcome

The cerebral oxygenation and metabolism profile will be better with propofol-based TIVA as compared to sevoflurane-based INHA in patients presenting for clipping of cerebral aneurysms.

Statistical analysis

An independent statistician blinded to the study protocol will perform statistical analysis. Data were manually entered into the pro forma by the investigators. It will not be analyzed to understand gender, caste, class, ethnicity, and race difference. Results will be analyzed using the Statistical Package for the Social Sciences, version 21 (SPSS Inc., Chicago, IL, USA). As appropriate, data were presented as mean and standard deviation or median (interquartile range). Continuous data normality will be evaluated with the Kolmogorov–Smirnov test. Qualitative data will be analyzed with the Chi-square or Fisher's exact tests. Intergroup comparison will be performed using an unpaired Student's *t*-test for parametric data and the Mann–Whitney *U*-test for nonparametric data. A paired Student's-*t*-test will be utilized for intragroup comparisons of the parameters. $P \leq 0.05$ considered statistically significant.

Ethical considerations

Our study involves the data collection from the monitors routinely used in all patients undergoing

Table 1: The derived study variables

Derived parameters
$AVDO_2=CaO_2-Cjv.O_2$
$CaO_2=(SaO_2 \times Hb \times 1.34) + (0.003 \times Pa.O_2)$
$Cjv.O_2=(Sjv.O_2 \times Hb \times 1.34) + (0.003 \times Pjv.O_2) \times Pa.CO_2$
$CEO_2=[CaO_2-CvO_2]/CaO_2$
$eCMRO_2=[(CaO_2-Cjv.O_2) \times Pa.CO_2)]/100$
$CBFe=1/[CaO_2- Cjv.O_2]$
$OEF=CMRO_2/[CaO_2 \times CBFe]$
$LOI=[AVDL \times 2.24]/AVDO_2$
$LGI=[AVDL \times 100]/[AVDG \times 2]$

$AVDO_2$: Arterial to jugular difference in oxygen content, AVDG: Arterial to jugular difference of glucose, AVDL: Arterial to jugular difference of lactate, $AVDO_2$: Arterial to jugular difference in oxygen content, CaO_2: Arterial oxygen content, $Cjv.O_2$: Jugular venous oxygen content, CBFe: Cerebral blood flow equivalent, CEO_2: Cerebral extraction ratio of oxygen, $eCMRO_2$: Estimated cerebral metabolic rate for oxygen, Hb: Hemoglobin, PaO_2: Partial pressure of oxygen in the arterial blood, LOI: Lactate oxygen index, OEF: Oxygen extraction fraction, $Pa.CO_2$: Partial pressure of carbon dioxide in the arterial blood, $Pjv.O_2$: Partial pressure of oxygen in the jugular venous blood, $Sjv.O_2$: Jugular venous oxygen saturation

surgical management of cerebral aneurysms. A trained neuro-anesthesiologist routinely performs USG-guided invasive accesses in an anesthetized patient after ensuring adequate depth and analgesia in all cerebral aneurysm surgeries. Since ours is a prospective observational study and the procedures performed are part of routine monitoring done in patients undergoing cerebral aneurysm clipping, no additional ethical concerns are unique to our study protocol. We plan to record the data obtained from the monitors to calculate the variables of cerebral oxygenation and metabolism. The process of obtaining informed consent described above is consistent with the Declaration of Helsinki and previous studies conducted in the Institute. To the best of our knowledge, there are no specific ethical issues unique to this project. No ethical clearance is sought from any other institution. The patients and relatives would be appraised of their right to participate in the study or withdraw consent at any time without adversely affecting their treatment. The samples collected for biochemical assessment will be discarded after obtaining the study results.

Dissemination of results

The results on the completion of the study will be presented to the scientific community through presentations and publications in peer-reviewed biomedical journals.

Confidentiality

Patients will be assigned a subject code corresponding to the hospital in-patient number, and the data will always be maintained on a computer with a password. Patient data will not be shared with anyone except the investigators. All steps will be taken to maintain the confidentiality of the patient. Patient details will not be revealed to the publisher if the proposed study is published in future. We do not expect any breach of trust or confidentiality.

Discussion

Cerebral aneurysm rupture resulting in aSAH presents a catastrophic neurologic insult with high mortality and morbidity.[1] Maintaining optimal perioperative cerebral oxygenation and metabolism is essential for good postoperative outcomes.[1-3] To date, there is a lack of evidence that suggests a strong recommendation for the preference of a particular mode of anesthetic technique during cerebral aneurysm surgeries. High-quality evidence regarding the effect of propofol-based TIVA or sevoflurane-based INHA on cerebral oxygenation and metabolism of patients undergoing cerebral aneurysm clipping is still lacking. Thus, identifying the ideal anesthetic agent with a better neurophysiological profile in terms of better intraoperative cerebral oxygenation and metabolism is critical to improving the postoperative outcome of these patients. Moreover, in our study, we will monitor cerebral oxygenation, metabolic state, and estimated cerebral blood flow, which will aid in the early detection of cerebral ischemia. This will help the attending clinician to do timely interventions even before the clinical symptoms set in, thereby improving the postoperative outcome.

Ghanem *et al*. evaluated the effects of TIVA based on propofol and INHA based on sevoflurane on cerebral oxygenation and metabolism profile in patients undergoing surgical management of cerebral aneurysm.[4] They observed that the cerebral blood flow equivalent (CBFe) and $SjvO_2$ were lower in the propofol group than sevoflurane. However, contrary to the term, propofol group used by the investigators, the TIVA group received additional midazolam infusion. As cited by the study investigators, the reason for the lower CBFe and $SjvO_2$ in the propofol TIVA group could be attributed to midazolam infusion, as it is known to exacerbate the effects of propofol on the cerebral circulation and cardiovascular system.[5,6] Gao *et al*. found that midazolam can reduce the adrenergic response to surgical stress without affecting the renin or cortisol response. This could cause a drop in systemic vascular resistance (SVR), and blood pressure in patients in whom SVR is already elevated, such as in chronic hypertension or aSAH.[6] In addition, the aSAH patients have a higher adrenergic drive than the non-aSAH group presenting for neurosurgery.[1] Moreover, midazolam's effect on cerebral blood flow, cerebral metabolic rate for oxygen ($CMRO_2$), and cerebral oxygenation needs to be considered. Thus, the above-mentioned reasons could have skewed the investigators' findings in favor of sevoflurane. Furthermore, the anesthetic level in both the TIVA and INHA groups was not standardized in this study as they did not use any DoA monitoring.[4] This could have resulted in variable dosing of anesthetics in either of the groups with varied effects on cerebral hemodynamics. In addition, the investigators did not study the postoperative complications and surgical outcomes in terms of cognitive function. The study population included only electively posted low-grade aneurysm (Fischer grade 1–3) patients with a Glasgow Coma Scale >12.

A randomized controlled trial (RCT) was done in patients undergoing surgery for aSAH, which compared propofol and desflurane for postanesthetic morbidity. They also studied the effects of these regimens on $SjVO_2$ in the perioperative period.[7] However, one of the fallacies of this RCT was that the investigators used 100% FiO_2 as they did not have the provision of air in the operating theaters, as stated by them. Moreover, $SjVO_2$ could be obtained in only 13 out of 33 patients in the propofol

group and 14 out of 35 patients in the desflurane group, based on which they concluded that the desflurane group had higher $SjVO_2$. Furthermore, only good-grade aSAH patients were included in this RCT, whereas altered cerebral metabolism and oxygenation secondary to raised intracranial pressure and cerebral autoregulatory failure are more likely to occur in poor-grade aSAH.[8] Thus, propofol and desflurane may have variable effects on cerebral physiology and might result in different outcomes and thereby is an area of future research.

In addition, the investigators administered mannitol 0.5 g/kg to all patients at the time of skin incision. Moreover, $PaCO_2$ was maintained at 32 and 35 mmHg, and these patients were further hyperventilated to a target $PaCO_2$ of 28–32 mmHg in the event of a brain swelling that persisted despite osmotic therapy. The alteration in CBF, which happens secondary to a change in $PaCO_2$, is termed as cerebrovascular reactivity to carbon dioxide (CVR-CO_2).[9] Studies have shown that both TIVA and INHA have variable effects on CVR-CO_2, and the effect of these agents on CVR also differs with many physiological and pathologic conditions.[10,11] This also might have influenced the variations observed by the authors.

Therefore, we have designed our trial to address the limitations pointed out by the previous trials. First, in our trial, the primary focus is to study the effects of TIVA based on propofol and INHA based on sevoflurane on the metabolic profile and cerebral oxygenation in aSAH patients presenting for aneurysmal clipping. Moreover, no previous research has used lactate oxygen index (LOI) as a marker of cerebral metabolism in clipping of aneurysm surgery under propofol-based TIVA and sevoflurane-based INHA. Previous studies utilized the parameters such as the estimated cerebral metabolic rate for oxygen, cerebral extraction ratio of oxygen, and CBFe as the markers of cerebral metabolism.[12] In our present study, we look forward to using an easily derived marker of cerebral metabolism, LOI, in addition to the other markers.[13,14] The average values of LOI are <0.03, and patients with low oxygen extraction have an LOI >0.08, secondary to the failure of aerobic metabolism in the brain and the resultant increased production of lactic acid.[14,15] Therefore, an intraoperative LOI >0.08 has been associated with poor outcomes in patients undergoing cerebral aneurysm clipping.[14] Furthermore, we would investigate whether the increase in CBFe due to the flow metabolism uncoupling offered by the inhalational would translate to a better metabolic profile and thereby influence the postoperative complications and patient outcome. For instance, patients with focal ischemia will have an elevated venous to arterial difference of lactate and LOI despite their cerebral perfusion pressure and $SjvO_2$ being within normal limits, resulting in a poor outcome.[14,15] Second, in our trial, the propofol TIVA group will receive only propofol as the anesthetic agent, and we standardize the DoA in both groups using a BIS monitor. Previously conducted studies were limited by the lack of a BIS monitor to assess the DoA and did not evaluate the postoperative outcome. We will study the postoperative outcome using mRS at discharge and GOS at 3 months in addition to the incidence of DCI.

Third, our trial will demonstrate the impact of burst suppression during temporary clipping on cerebral metabolism and oxygenation.[16,17] We aim to target a BSR of 50% during the phase of temporary clipping in both the groups. None of the previous trials have explored this aspect of perioperative monitoring. Fourth, to overcome the confounding effects of $PaCO_2$ and osmotherapy on cerebral oxygenation and metabolism, we have standardized the $PaCO_2$ targets as 35–40 mmHg and avoided the routine use of mannitol in our trial. Also, the previous studies have included only good-grade aSAH, and there is a scarcity of studies conducted in this regard on high-grade aneurysms and poor-grade aSAH. Our proposed research will include all severity grades of cerebral aneurysm patients posted for clipping in the neurosurgery operation theater.

Strengths of our trial

- Standardization of the anesthetic protocol and the DoA monitoring in both the study groups
- Inclusion of poor-grade SAH to see if the effect of TIVA-based brain relaxation and persistent flow metabolism coupling would extrapolate to a better metabolic profile and outcome
- Avoiding the confounding effects of osmotic agents and hyperventilation on cerebral oxygenation and metabolism by administering osmotherapy in both groups and targeting intraoperative ventilation to a set $PaCO_2$ value
- Here, we plan to study all the essential neurophysiological parameters, namely, cerebral blood flow, oxygenation, and metabolism, and the effect of pharmacological burst suppression during temporary clipping
- Attempt to validate LOI in aSAH as a clinically useful marker of cerebral oxygenation and metabolism.

Limitations

- This is a pilot study conducted at a single institution
- The study does not include patients presenting for neuro-interventional management of aSAH, such as coiling or flow diverter therefore, the findings of this trial cannot be extrapolated to patients undergoing therapeutic neuro-intervention for aSAH.

Trial status

The trial has been initiated with the patient enrolment from May 2023. The enrolment of participants continues at the time of manuscript submission.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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