Brief Report

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Comparison of Intraoperative Hypotension Outcomes with and Without Hypotension Prediction Index Tool in Patients Undergoing Brain Tumour Surgery: A Study Protocol for a Randomised Controlled Trial

Thomas Francis, Sriganesh Kamath, Rajeeb Mishra Kumar, Dhritiman Chakrabarti

Abstract:

Intraoperative hypotension (IOH) is a common occurrence during general anaesthesia for neurosurgery. Hypotension Prediction Index (HPI) is a recently available novel tool that uses arterial waveform features to predict IOH. This study aims to evaluate the role of HPI-integrated haemodynamic management protocol on IOH outcomes during brain tumour surgery. This is a single-centre, parallel-group, randomised controlled trial, approved by the Institute's Ethics Committee and the Clinical Trial Registry of India, and funded by the Indian Council of Medical Research. Consenting and eligible adult patients undergoing brain tumour decompression surgery will be randomised to either HPI-guided ($n = 90$) or conventional ($n = 90$) haemodynamic management in a 1:1 allocation ratio using a computerised random allocation sequence. Our primary outcome is the duration of IOH. Our secondary outcomes are the time-weighted average of IOH of mean arterial pressure < 65 mmHg, and incidence, severity, and timing of IOH. We will collect data about adverse effects of IOH, including vasopressor use, myocardial ischaemia, acute kidney injury, emergence and postoperative delirium, duration of intensive care unit, and hospital stay. If our study results demonstrate a beneficial effect of HPI, this will change current anaesthetic practice and approach to IOH, and improve perioperative outcomes after brain tumour surgery.

Key Words:

Brain tumours, hypotension prediction index, intraoperative, machine learning, monitoring, neurosurgery

Key Message:

This RCT will demonstrate the utility of the hypotension prediction index in reducing intraoperative hypotension during brain tumour surgery and its impact on perioperative patient outcomes.

Department of Neuroanaesthesia and Neurocritical Care, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India

Address for correspondence:
Dr. Sriganesh Kamath, Department of Neuroanaesthesia and Neurocritical Care, National Institute of Mental Health and Neurosciences, Bengaluru - 560 029, Karnataka, India.
E-mail: drsri23@gmail.com

Intraoperative hypotension (IOH) is a common but important complication during anaesthesia and surgery. It is estimated that up to 88% of patients manifest with at least one episode of IOH hypotension (mean arterial pressure [MAP] <65 mmHg).[1] IOH can lead to various adverse consequences such as delirium, acute kidney injury (AKI), myocardial ischaemia, and stroke.[2,3] These complications are particularly deleterious in patients undergoing brain surgery. Preventing the occurrence and promptly correcting IOH is therefore critical to improve perioperative outcomes. The conventional approach to IOH has been reactive, implying intervention is done after the hypotension has occurred. With recent advances in artificial intelligence and machine learning (AIML), we can predict undesirable changes in physiological parameters before their occurrence.[4] Hatib *et al*.[5] developed an algorithm using AIML from the arterial pressure waveform analysis to predict hypotension before blood pressure decreases. The hypotension prediction index (HPI) algorithm model has used the definition of hypotension as MAP < 65 mm Hg for at least 1 minute for precision

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purposes. The HPI tool has been validated and has high sensitivity and specificity. The HPI value ranges from 0 to 100, with higher values indicating an increased risk of developing hypotension in the near future. Since its commercial availability, HPI has been evaluated in different surgical procedures. However, only a few randomised controlled trials (RCTs) have compared HPI with a conventional blood pressure-based approach for IOH.[6-13] These trials are few, had small sample sizes, and reported conflicting findings, necessitating the conduct of this large RCT.

The primary objective of this RCT is to compare the duration of IOH in the HPI and the conventional group. The secondary objectives are to compare the time-weighted average (TWA) of IOH of MAP < 65 mmHg and the incidence, severity, and timing of IOH in both groups. Our tertiary exploratory objective is to compare the adverse effects of IOH, including vasopressor use, myocardial ischaemia, AKI, emergence and postoperative delirium, durations of intensive care unit (ICU) and hospital stay, and cost analysis.

Methods

This is a prospective, parallel-group, single-centre, public-funded RCT that will be conducted in the neurosurgery operating room of a tertiary academic university hospital. Our study was approved by the Institute's Ethics Committee on 5th June 2024 (No. NIMH/47th IEC BS and NS DIV./2024). This trial is registered prospectively with the Clinical Trial Registry-India (vide registration number CTRI/2024/07/069939 on 04/07/2024) before the recruitment of the first patient. Informed written consent from trial participants will be obtained by one of the investigators before patient recruitment. The planned study period is two years. Trial insurance has been obtained for all the study participants, and the investigators are covered with trial indemnity. This study protocol follows the SPIRIT 2013 (Standard Protocol Items: Recommendations for Interventional Trials) statement. Figure 1 depicts the flow of the participants in our study.

All patients who will be admitted to our hospital with a brain tumour and posted for tumour decompression will be assessed for recruitment. They will be enrolled in the trial if they fulfil the inclusion criteria and provide written informed consent to participate in the study. The patient and the data analyst will be blinded to the study intervention. Since the HPI tool is visible to the attending anaesthesiologist, he/she will not be blinded to the study interventions.

Our inclusion criteria are age between 18 and 65 years of either gender, American Society of Anesthesiologists physical status (ASA PS) I and II, undergoing elective surgery for excision of brain tumours of size >4 cm, type of brain tumours including intra-axial and extra-axial involving both supratentorial and infratentorial locations with an anticipated intraoperative bleeding of >500 ml. We will exclude patients if they have preexisting hypotension, cardiac failure, uncontrolled hypertension, arrhythmia, cardiac shunts, aortic stenosis, undergo emergency surgery, undergo surgery in a sitting position, are pregnant, or refuse consent for study participation.

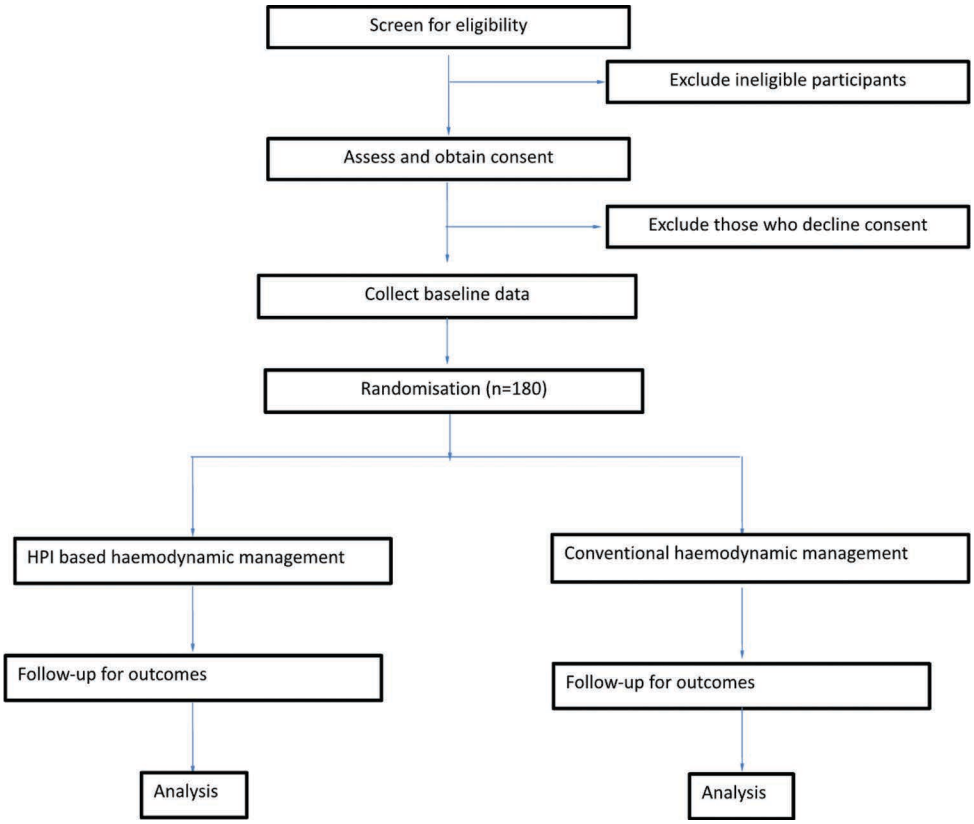

Figure 1: Flow of the participants in our study

Block randomisation with a block size of four will be done by a co-investigator using a computer-generated random number sequence. Randomisation will be done in a 1:1 allocation ratio to either the HPI-guided or the conventional approach group. Randomisation code will be revealed to the study investigator after the patient recruitment is completed centrally by telephone, just before implementation to maintain allocation concealment.

In the operating room, standard ASA monitoring [heart rate (HR), peripheral oxygen saturation (SpO2), end-tidal carbon dioxide (ETCO2), and core temperature] will be applied for all patients. In addition to the standard monitoring, Entropy or BIS (Bispectral index) sensors will be used to monitor the depth of anaesthesia. An arterial line will preferably be secured in the radial artery for invasive blood pressure monitoring under local anaesthesia before anaesthesia induction. After obtaining baseline recordings, intravenous anaesthesia will be induced with a standard technique: 1.5 mg/kg preservative-free 2% lignocaine, 1-2 μg/kg fentanyl, and 5 mg/kg thiopentone, and 0.1 mg/kg vecuronium will be administered to facilitate tracheal intubation. Anaesthesia will be maintained with oxygen, air, and an inhalational agent (sevoflurane or desflurane) at a minimum alveolar concentration (MAC) of 1 ± 0.2 to achieve and maintain a BIS/entropy value of 40-60. For surgeries requiring intraoperative neuromonitoring, the anaesthesia technique will include a combination of intravenous anaesthesia with propofol and an inhalational agent (MAC < 0.5) or total intravenous anaesthesia with propofol. However, the depth of anaesthesia will be maintained similarly in all patients in both groups, to minimise the contribution of anaesthesia technique to IOH. Opioids (fentanyl or morphine) will be used for analgesia.

As part of the study, the HPI group will have an additional Acumen transducer connected to the HemoSphere monitor (Edwards LifeSciences, Irvine, CA, USA) with the HPI software. When the index is ≥85, the HemoSphere monitor alerts the operator, and a secondary screen is revealed. The secondary screen displays haemodynamic variables (MAP, HR, stroke volume (SV), cardiac output (CO), systolic slope calculated as increase in systolic pressure divided by the duration of systole as an indicator of left ventricular contractility (dP/dt), stroke volume variation (SVV) as an indicator of preload, and dynamic arterial elastance (Eadyn) which is pulse pressure variation (PPV) divided by SVV as an indicator of afterload. These parameters provide information about the likely underlying cause of the predicted hypotension. All these parameters, including the HPI, are updated every 20 seconds. The attending anaesthesiologist will be informed about the study protocol before the initiation of the procedure. In the HPI group, when the HPI goes >85, a specific algorithm will be followed [Figure 2]. This will allow us to identify the cause of hypotension and act accordingly. In case of decreased preload (SVV >13%), fluids will be administered, while for decreased contractility (dP/dt <400 mmHg/sec), dobutamine will be initiated, and for decreased afterload (Eadyn <0.9), vasopressors will be initiated.

In the conventional group, standard management with invasive blood pressure monitoring will be followed. Administration of fluids, vasopressor, or inotrope will be guided by the haemodynamic parameters displayed on the multi-parameter patient monitor at the discretion of the attending anaesthesiologist. The common causes of hypotension, including post-induction hypotension, bleeding, myocardial dysfunction, low HR, and anaesthetic agents, will be identified, and standard management will be adopted by the attending anaesthesiologist. The management will involve giving fluids and a vasopressor bolus in case of post-induction hypotension, giving fluids, blood products, and a vasopressor for bleeding, giving inotropes for possible myocardial dysfunction, atropine for bradycardia, and titration of anaesthetic agents, fluids, and vasopressors for hypotension caused by anaesthetic agents.

Haemodynamic measurements from the HemoSphere monitor will be exported via USB as Microsoft Excel (Microsoft Corporation, Redmond, WA, USA).xls files. In both groups, hypotension data will be collected from the Anaesthesia Information Management System (Centricity™ Perioperative Anaesthesia, GE Healthcare) and other data from the patient's medical records.

The primary outcome of the trial will be the duration of IOH in both the HPI group and the conventional group. The secondary outcome will be the TWA of IOH, defined as the depth of hypotension (mmHg) below a MAP of 65 mmHg multiplied by the time spent with MAP <65 mmHg (in minutes) divided by the total duration of surgery (in minutes). Our secondary outcome will include the incidence of IOH, defined as the number of hypotensive events during the intraoperative period (beginning of anaesthesia to the end of anaesthesia). A hypotensive event is defined as a reduction of MAP to <65 mmHg for at least 1 minute. The duration of the hypotensive event will end when the MA*P* value is normalised. We will compare the severity of hypotension by calculating the TWA of IOH below 60 mmHg and 55 mmHg of MAP between the two groups. We will compare the timing of IOH into two time periods (pre-surgical and surgical phase).

We will compare the volume of intraoperative fluids (crystalloid and colloid), erythrocyte transfusion, cumulative dose of the vasoactive medications, anaesthetics, and analgesics, blood loss, and urine output between the two groups. We will also collect details regarding the following outcome measures – intraoperative myocardial ischaemia event (ST-segment values < or >2 mm for atleast 1 minute),[14] AKI (increase in serum creatinine by >0.3 mg% as per AKI Network criteria), emergence (Riker sedation agitation scale) and postoperative delirium (confusion assessment method), new-onset motor deficits (perioperative stroke), length of ICU stay, and duration of hospital stay.

There is enough evidence to suggest that IOH can affect clinically important outcomes of myocardial ischaemia,[15] AKI,[16] delirium,[17] and perioperative stroke.[18] In this study, we expect HPI-guided management to have a lower incidence of IOH and consequently a lower incidence of IOH-related complications. The findings of our study can inform the sample size needed for future RCTs where these patient-important outcomes are evaluated as a primary outcome. We will also calculate cost-effectiveness with the use of HPI. The cost-effectiveness will include the cost of fluids, vasopressors,

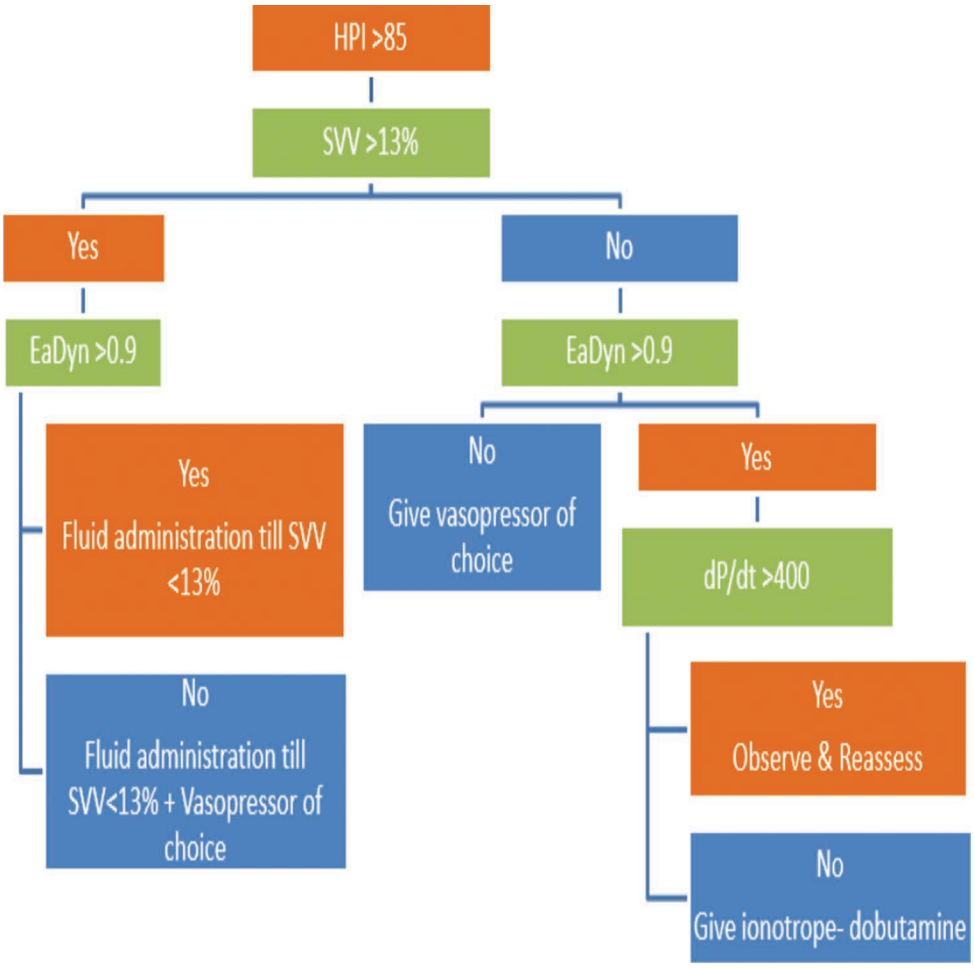

Figure 2: Algorithmic approach to intraoperative hypotension assessment and management

blood transfusions, ICU and hospital stay, and the cost of the HPI sensor.

For sample size calculation, we used a study by Pouska *et al*.[13] which compared HPI with standard care (20 per group) with regards to IOH during supratentorial brain surgery. The proportion of patients who never experienced hypotension was significantly lower in the HPI group (50% vs 80%). Using this study, a Z test was applied with a power of 0.95 and an α error probability of 0.01, and the sample size was calculated to be 87 per group. To adjust for the likely attrition, we inflate the sample size to 90 patients in each group.

For data analysis, continuous variables will be displayed as either mean and standard deviation for values with a Gaussian distribution, or median and interquartile range, or 95% confidence interval for data that does not follow a normal distribution. The normality of distribution will be assessed using the Shapiro-Wilk test. Categorical variables will be displayed as counts and percentages. Differences in independent continuous variables between the groups will be tested for statistical significance using the Student *t*-test for independent samples or the Mann-Whitney U test, depending on the distribution of data. *P* values < 0.05 will be considered statistically significant. The software package R will be used for statistical analysis and data visualisation.

Results

The current study aims to evaluate the role of HPI integrated with a haemodynamic management protocol on IOH and IOH-related perioperative complications during brain tumour surgery. The first patient was enrolled on 8th July 2024. At the time of manuscript submission, enrolment of participants continues. The final results of the completion of the study will be communicated to the scientific community through conference presentations and scientific publication in a peer-reviewed biomedical journal.

Discussion

Hypotension is common during surgical procedures. To date, only one large sample RCT has been published.[11] However, this study excluded neurosurgical patients and found no significant difference in IOH with the use of HPI. The remaining seven RCTs,[6-10,12,13] having small sample sizes of fewer than 50 patients in each group, have found HPI to be useful. Of these, only one small study ($n = 40$) was done in neurosurgical patients,[13] and it did not find a significant difference between HPI and control groups for the average duration of hypotensive period, cumulative time of hypotension assessed by area under the curve (AUC) and TWA, and per patient incidence of hypotension, though the number of patients who

never experienced hypotension was lower with HPI. Since the findings vary across studies, have the potential for bias due to conflict of interest for the investigators with device manufacturers, and are limited due to small sample sizes, there is a need for this study to establish the utility of HPI in day-to-day clinical practice for managing IOH. Additionally, as per a recent systematic review and meta-analysis of eight RCTs,[19] the cumulative sample size of 564 was less than the required sample size of 664 on trial sequential analysis (TSA), because of which a false-positive, beneficial effect of HPI on IOH is possible. As this finding suggests that future results may change with additional trials, we are undertaking this large sample-sized trial funded by an independent agency (Indian Council of Medical Research) and adding a cost assessment as one of the outcomes, which is the novelty of this study. This way, we will be able to better inform about the clinical utility of HPI, especially in resource-limited settings such as developing countries. However, our study is limited by a single-centre nature and only brain tumour surgery patients as the study population, which may limit the generalisation of our findings.

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Conflicts of interest

There are no conflicts of interest.

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