TITLE: PERIOPERATIVE ANALGESIC MANAGEMENT USING THE CONVENTIONAL VERSUS REGIONAL NERVE BLOCK IN CRANIOTOMY SURGERIES IN LOWER MIDDLE-INCOME COUNTRIES.

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STATEMENT OF COMPLIANCE:

This study is in compliance with the Good Clinical Practice (GCP) Guidelines.

Introduction:

In craniotomies, optimal pain management enhances haemodynamic stability by lowering the intraoperative and postoperative surgical stress response[1]. According to extensive research over 55% of patients have moderate to severe postoperative pain in the first 24 hours post craniotomy[2]. Inadequate intraoperative and postoperative pain control is known to cause serious short-term and long-term sequelae[3], such as cerebral hyperemia, brain swelling[4], intracranial hemorrhage[5], agitation along with risk of development of chronic pain syndrome, with incidence as high as 25% according to some literature. There is currently no generally accepted opinion

regarding which analgesic method is the most suitable for the perioperative pain treatment of patients undergoing elective brain tumor surgeries[6].

Nonetheless, opioids continue to be considered the cornerstone for treating moderate to severe pain following a craniotomy[7]. However, the primary clinical concerns with opioids are still their side effects, which include nausea, vomiting, and respiratory depression, as well as the possibility of over-sedation that might impair neurological assessment and prevent the early diagnosis of surgical problems[8].

Apart from the diverse systemic pharmacologic treatment, the century-old scalp nerve block (SNB) approach is still employed and being researched as an alternate option for patients having craniotomy procedures[9]. It has been noted that using SNB before surgical incision lowers the likelihood of perioperative arterial hypertension, suppresses the haemodynamic reaction to unpleasant stimuli, maintains intraoperative haemodynamics, lowers postoperative pain scores and amount of opioid consumption[11] and facilitates a quicker and more seamless emergence[10]. Thus, the aim of our study is to compare the systemic opioids with the pre-incision bilateral scalp nerve block for the intraoperative noxious stimuli and postoperative pain management in patients undergoing craniotomy surgery.

Rationale of Study:

The scalp nerve block delivers stable intraoperative hemodynamics on various noxious stimuli and facilitates smooth emergence along with the better postoperative pain management, narcotic consumption and narcotic side effects like sedation, nausea and vomiting.

Risks and Benefits of Study:

Participation in this study will aid in determining the efficacy of bilateral scalp block, adding to the body of knowledge, justifying the study's validity in the future, and encouraging safer procedures with reduction in narcotic consumption and narcotic side effects like sedation, nausea and vomiting.

Risks of this study include pain, hematoma, swelling of the upper eyelid, local toxicity, intraarterial injection and undesired facial nerve block brought about by the methods and procedures of the research.

Objectives:

The primary objective of this research is to evaluate the effectiveness of systemic opioids with pre-incision bilateral scalp nerve block for the intraoperative hemodynamic variables (Heart rate, Systolic blood pressure, diastolic blood pressure, Mean arterial blood pressure) on various noxious stimuli such as on intubation, 3 minutes after intubation, prior to scalp nerve block, 3 minutes after scalp nerve block, before head pinning, 1 and 3 minutes after head pinning, at surgical incision, 3 minutes after skin incision, during bone and periosteum dissection, Dural opening, Dural closing, skull bone closure, skin closure in patients undergoing for the supratentorial craniotomy. The secondary objective of this research is to evaluate the patients' pain, morphine intake, sedation, nausea, and vomiting within the initial 24 hours following surgery.

Hypothesis:

The scalp nerve block performed at the pre-incision in craniotomy surgery would attenuate the intraoperative noxious stimulatory response and improve the postoperative pain scores, along with cutting down the use of opioids and the associated adverse effects.

Material & Method:

Study Design:

Randomized Control Trial

Setting:

The study will be conducted at the main operating room of Aga Khan University Hospital Karachi.

Duration of Study:

Three to six months after the approval of synopsis.

Sampling Technique:

Non-Probability Consecutive Sampling.

Study Population:

Inclusion Criteria:

- Age 18 years to 75 years,
- American Society of Anesthesiologists class I-III, ● Scheduled for supratentorial craniotomy.

Exclusion Criteria:

- Patient with Glasgow Coma Score (GCS) of less than 15,
- Inability to understand the Visual analog scale (VAS)
- Allergic to study drugs (Morphine and local anesthetics) ● Patient chronically treated with narcotic medications.
- History of Liver dysfunction

Data Collection Methodology:

Once the approval is taken from the Departmental research committee, Ethical review committee and College of Physicians and surgeon Pakistan, and the study participants' written informed consent. Patients who meet the requirements will be considered for participation and their primary surgeon will be informed of such. Patients whose surgeon agrees for their participation will be handed over the consent form.

Consent will be taken from patients willing to participate voluntarily in the ward a day before the procedure by the primary investigator or the co-investigator in a separate room with minimal interruptions in patient’s native language or with the help of translator if any language barrier is present. The entire process will be explained in detail with possible adverse events.

Patients will have the option of accepting or declining the invitation to participate in this study, and routine standard practice will not change in case of refusal to participate.
All patients will be examined, day before surgery and will be explained in detail for the use of visual analogue scale (VAS) for pain assessment (A number of 0 indicates no pain, and a score of 10 indicates the most intense form of pain), to measure the extent of pain. Additionally, the use of the patient-controlled analgesia (PCA) system for post-surgical pain management will be explained to the patients. No patient will be premedicated with sedatives.

All study subjects will be divided into two groups: group M (systemic morphine), and group S (bilateral scalp nerve block). Once the standard ASA monitors are applied (ECG, NIBP, SPO_2), the baseline blood pressure and heart rate will be recorded. Using computer-generated simple randomisation, patients will be divided into two groups at random in a 1:1 ratio: group S (bilateral scalp nerve block), and group M (Systemic Morphine). Anesthesia induction in group S (Scalp Nerve Block) will be performed with Propofol 2mg kg^{-1}, fentanyl 1.5-2 μg kg^{-1}, and cisatracurium 0.15mg kg^{-1}. The group M (Systemic Morphine), anesthesia induction will be performed with Propofol 2mg kg^{-1}, morphine 0.1mg kg^{-1}, and cisatracurium 0.15mg kg^{-1}. After intubation in both study groups, the arterial waveform monitors and temperature probe will be used and anesthesia will be maintained using isoflurane (minimum alveolar concentration, 0.7-1.2), in oxygen and nitrous oxide. Cisatracurium infusion initiated at 0.003 mg kg^{-1} per minute to maintain the muscle relaxation throughout surgery and at the end of procedure, it will be reversed with neostigmine 0.04 mg $kg^{-1}$and glycopyrrolate 0.006 mg kg^{-1}. Patient will be given intravenous paracetamol 1 gram at induction along with the dexamethasone 4-8 mg. Routine intravenous ondansetron 4-8 mg will be administered 30 minutes prior to end surgery for emesis prophylaxis.
In Group S (intervention group), the mixture of local anesthetics including the lidocaine 0.1%, ropivacaine 0.25%, adrenaline 1:200000, and dexamethasone 4 mg. Both, SNB block drugs preparation and SNB block, will be carried out by the primary investigator or the assigned anaesthesiologist in the scalp block group after arterial line insertion. The bilateral SNB block including the Supraorbital and Supratrochlear nerve will be infiltrated with 2 milliliters (mls) on each side. Auriculotemporal nerve will be infiltrated with 3 mls each side. Zygomaticotemporal nerve will be infiltrated with 4 mls on each side. Greater auricular nerve will be infiltrated with 3 mls on each side. Greater occipital and Lesser occipital nerve will be infiltrated with 4 mls on

each side. In group M, the only pin side infiltrated with 2 mls on each pin with similar drug dilution. The surgeon will be allowed to infiltrate the incision line with 1% lidocaine plus adrenaline 1:200000 prior to skin incision in both study groups. The study outcome parameters including the intraoperative hemodynamic variables (Heart rate (HR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial blood pressure (MAP)), will be measured at baseline, on intubation, 3 minutes after intubation, prior to scalp nerve block, 3 minutes after scalp nerve block, before head pinning, 1 and 3 minutes after head pinning, at surgical incision, 3 minutes after skin incision, during bone and periosteum dissection, Dural opening, Dural closing, skull bone closure and skin closure. Mean arterial blood pressure and heart rate variations above 20% of the initial values will be responded initially by adjusting the maximum isoflurane end tidal alveolar concentration up to 1.2%, if still MAP and HR remained greater the fentanyl 0.5 mg kg^{-1} bolus will be administrated as rescue analgesic. Both study groups will receive patient control analgesia (PCA) pump for 24 hours post surgery. The PCA pump will be initiated in post anesthesia care unit (PACU), with drug dilution of morphine 1mg/ml in normal solution. PCA will be configured to provide a 0.5 mg bolus dose on demand, with a 10-minute lockout period and a 24-hour maximum dose. The visual analogue scale (VAS), which has a score range of 0 to 10 (0 = no pain = 10 severe pain), will be used to assess pain at different time interval such as on arrival in PACU, 30 minutes, 1, 2, 4, 6, 12, 18, 24 hours. In PACU, the addition to PCA, morphine will be supplemented as rescue analgesia to decrease the pain score below 4. The other parameters such as sedation score using on four-point scale (1 = awake and communicative, 2 = asleep, responds to normal speech, 3 = asleep, responds to pain, 4 = deeply sedated), and nausea vomiting score using the four-point scale (0 = no nausea and vomiting, 1 = mild nausea, 2 = severe nausea with retching, 3 = vomiting), will be measure for 24 hours postoperatively. The patient's study parameters will be collected by an independent data collector assigned in the operating room and postoperatively by a pain nurse, the data collector and patient will be blinded to the study groups. Coding will be used for documentation instead of mentioning the drugs used or intervention done to ensure blinding from the data collector.

Sample Size:

The sample size was calculated using STATA version 14.0 software. A test (two-sided) comparing two independent means was used. Considering that the VAS mean±SD for the first 24

hours following surgery would be 4.1±3.1 for the control group and 1.9±2.6 for the intervention group, it was calculated that 28 patients in each group would be needed to reach 80% power at the 5% significance level to show a difference of 50% on the VAS[13]. To reduce the impact of data loss, we will enroll 31 patients in each group, assuming a 10% dropout rate.

It was also an estimated sample based on the study [14], the baseline mean±SD of MAP (mm Hg) for Group Block was 68.9 ± 4.0 while Group was Morphine 72.2 ± 3.6. with a 10% drop rate, 24 patients in each group would be required, using a 5% α (level of significance) and 20% β (power of test) with a confidence interval of 95%.

The highest sample size (31 patients per group) was decided to recruit the participants in the study.

Data Analysis Procedure:

The R software (version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria) will be used to analyze the data. A comparative analysis will be conducted between Group M (Systemic Morphine) and Group S (Intervention) to identify any variations that are statistically relevant. The normality assumption for numerical variables, such as age, weight, height, duration of surgery and anesthesia, intraoperative hemodynamics and postoperative numerical variables, and VAS scoring, etc, will be tested using the Shapiro-Wilk test. For normally (non-normally) distributed variables, the mean±standard deviation (median± interquartile range) will be computed and will be analyzed between groups using an unpaired independent t-test (MannWhitney). Categorical data, such as sex, diagnosis, type of craniotomy, and craniotomy incision, will be reported using frequency and percentage and compared using either the Chi-square or Fisher's exact test. A significance level of $P \leq 0.05$ will be used.

Data and Record Handling:

Data monitoring will be the responsibility of the principal Investigator. The Forms will be checked on a regular basis for accuracy, legibility, and completeness. Hard copies of the data will be placed under lock and key and soft copies will be password protected.

All the study data would be discarded as per AKUH's 7 year data retention policy**.** After completion of the study results will be shared with patients upon request. Institutional and other regulatory bodies will have direct access to source data for monitoring and audit purposes.

Adverse Events:

Adverse Events are defined as 'Any untoward medical occurrence in a trial patient to whom a research treatment or procedure has been administered, including occurrences which are not necessarily caused by or related to that treatment or procedure.

The patients will be monitored for possible scalp block complications such as hematoma, swelling of the upper eyelid, local toxicity, and undesired facial nerve block. Any immediate complication will be recorded and will be managed according to the standard management protocol in contact with the primary investigator or co-investigator.

Patients will be followed and monitored till the resolution of symptoms and discharge and all adverse effects will be reported to the ethical review committee in the progress report.

Serious Adverse Events

Serious Adverse Events are defined as an untoward event that: Results in death; Is life-threatening; Requires hospitalization or prolongation of existing hospitalization; Results in persistent or significant disability or incapacity; Or is otherwise considered medically significant by the Investigator.

All SAEs will be reported within 24 hours to the ERC, and hospital management through online incident report.

Ethical Considerations:

Written and informed consent will be taken from patient or their legal representative in surgical wards before surgery and a copy of the informed consent will be given to the patients. The privacy of patients will be ensured by using private and secure settings where the conversation cannot be overheard or interrupted. Access to data will be limited to only authorized researchers directly involved in the study.

Confidentiality of the patient and data will be maintained by assigning a number for each patient data, electronic data will be password protected and data on hard copies will be kept in a lock and

key. Any potentially identifying information will be removed or altered from the interview transcripts during data analysis. All the study data would discarded as per AKUH's 7 year policy. After completion of the study results will be shared with the patients upon their request. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting. Institutional and other regulatory bodies will have direct access to source data for monitoring and audit purpose.

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