Trial Protocol

Non-opioid versus Opioid Peri-operative Analgesia In Neurosurgery (NOPAIN): Study protocol for a multi-centric randomised controlled trial

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ABSTRACT

Background and Aims: Many patients suffer from post-operative pain after neurosurgery despite using intra-operative opioids. Opioid side effects are problematic in neurosurgical patients. Hence, non-opioid alternatives for the management of nociception and pain are needed. Previous studies comparing opioids with non-opioids in the neurosurgical population were few, from single centres, of small sample sizes and were equivocal in findings, which prevented change in clinical practice. To overcome these limitations, we are conducting a multi-centre trial with objectives to compare intra-operative rescue opioid requirements and post-operative pain scores (primary objectives), adverse events, quality of recovery from anaesthesia, quality of sleep and patient satisfaction during hospital stay, and persistent post-surgical pain and quality of life at 3 and 6 months (secondary objectives) in patients receiving opioid and non-opioid analgesia for brain tumour surgeries. **Methods**: This study protocol describes the methodology of a multi-centre randomised controlled trial. Ethics committee approval has been obtained from all five centres, the trial has been registered with the Clinical Trial Registry- India, and insurance has been obtained for this investigator-initiated funded study. In patients undergoing supra-tentorial brain tumour surgery (population), we will compare fentanyl (intervention) 1 μg/kg/h with dexmedetomidine (comparator) 0.5 μg/kg/h administered during surgery with regards to intra-operative rescue opioid requirement and post-operative pain (primary outcomes). **Results**: We describe the study protocol of the multi-centre trial (protocol version 2, dated 29/01/2022). The first patient was recruited on 19/10/2022, and we will complete recruitment before March 2024. **Conclusion**: We expect our study to establish dexmedetomidine as an effective non-opioid analgesic vis-à-vis opioids in the neurosurgical population.

Key words: Analgesia, brain tumour, dexmedetomidine, neurosurgery, non-opioids, opioids, quality of life, quality of recovery, quality of sleep, trial protocol

INTRODUCTION

Post-operative pain is seen in up to 70% of patients undergoing intracranial neurosurgery despite using potent opioids.[1,2] In the Indian scenario, structured pain assessment and use of post-operative opioids for pain management in neurosurgical patients are limited compared to developed nations, which

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may result in different incidences of post-operative pain.[3] The undesirable side effects of opioid use, such as post-operative nausea and vomiting (PONV), gastrointestinal dysmotility, urinary retention, prolonged recovery, itching, post-operative sedation, and respiratory depression, are likely when opioids are used in high doses during surgery.[4] Non-opioid analgesics/adjuvants have been found to provide comparable pain relief in patients undergoing bariatric[5] and laparoscopic surgeries.[6] In neurosurgical patients undergoing craniotomies, non-opioid analgesics/adjuvants such as dexmedetomidine, an alpha-2 agonist, have been found to reduce anaesthetic and opioid requirements.[7,8] Recently, systematic reviews of randomised controlled trials (RCTs) comparing opioid and non-opioid analgesia in patients undergoing craniotomies showed equivalence of both analgesia techniques.[9,10] However, evidence is insufficient to routinely adopt non-opioids as the preferred analgesic for brain surgery because of the low sample sizes, high risk of bias, and significant heterogeneity in the primary studies. In our pilot RCT, we demonstrated the feasibility of performing a larger trial and established the non-inferiority of dexmedetomidine to fentanyl regarding post-operative pain and intra-operative rescue opioid requirements.[11] The stress response to surgery with both techniques was also comparable.[12]

We intend to conduct this multi-centre trial to confirm whether dexmedetomidine will be an effective and safer alternative to opioids for peri-operative pain management in patients undergoing intracranial neurosurgeries. We hypothesise that non-opioid analgesia is superior to opioid analgesia regarding rescue analgesia requirements and post-operative pain and may be better regarding adverse events, quality of recovery, sleep, and satisfaction, with similar long-term outcomes. The primary objectives of this trial are to compare the a] intra-operative rescue opioid requirements and b] post-operative pain scores in patients receiving an opioid and a non-opioid as the primary systemic analgesic for brain tumour surgeries. Our secondary objectives are to study and compare 1] drug-related adverse events, 2] quality of recovery from anaesthesia, including emergence delirium, 3] quality of sleep and patient satisfaction, and 4] persistent post-surgical pain and quality of life at 3 and 6 months.

METHODS

This prospective, multi-centre, randomised, parallel-group clinical trial will be conducted at five tertiary care institutions (National Institute of Mental Health and Neurosciences, Bengaluru; Christian Medical College, Vellore; Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry; Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum; and Nizam's Institute of Medical Sciences, Hyderabad) in India with high volumes of neurosurgical procedures. The research proposal for this trial has received approval from the institutional ethics committees (IECs) of all five recruiting centres [vide approvals numbers NIMHANS/34th IEC (BS and NS DIV)/2022 dated 08/02/2022, SCT/IEC/1872/APRIL/2022 dated 02/06/2022, CMC Ref: IRB Min. No. 14501 [INTERVEN] letter dated 13/05/2022, JIP/IEC/2022/050 dated 10/06/2022, and Review letter no. EC/NIMS/2963/2022, PBAC no. 1396/2022 dated 03/03/2022]. This trial was registered prospectively with the Clinical Trial Registry-India (vide registration number CTRI/2022/09/045705, registered on 20/09/2022, https://ctri.nic.in/) before the recruitment of the first patient. Written informed consent will be obtained from the participants of this study separately for participation in the research and use of anonymised data for dissemination of findings as academic presentation and scientific publication. The planned study period is 2 years (October 2022–September 2024). The study will be carried out as per the principles of the Declaration of Helsinki, 2013.

All consecutive consenting eligible adult patients of either gender, aged 18–65 years, scheduled for elective craniotomies for supratentorial brain tumours with a Glasgow Coma Scale score of 15 will be included in this trial. We will exclude patients if they do not consent or if they have a history of significant ischaemic heart disease, cardiac failure, heart block or arrhythmia, uncontrolled hypertension and diabetes mellitus, undergoing emergency surgery, receiving long-term drugs to manage pre-existing pain, previous cranial surgery, allergy to study drugs and opioid dependence. Figure 1 depicts the flow of the participants in our study.

One project associate at each centre will screen potential participants posted for elective craniotomies and perform the enrolment after obtaining informed consent in the patient's language. The primary investigator from the hub centre will perform the randomisation (in a predetermined block of 6 for each centre) using a computer-generated random number

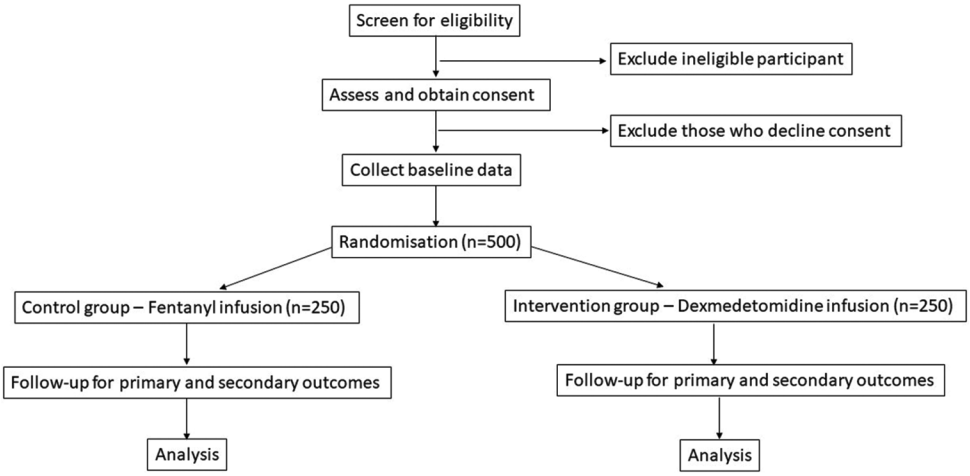

Figure 1: Diagram showing the flow of the participants in our study

table with a 1:1 allocation ratio. The randomisation details for each centre will be shared from the remote central randomisation facility with the principal investigator at the hub centres, who will reveal the allocation sequence to the anaesthesia technician or peri-operative nurse (not involved in the study) at each centre just before implementation (to maintain allocation concealment and prevent selection bias). This person will prepare study drugs as per the allotted sequence number and assign them to the patients. To ensure blinding, study drugs in both groups will be prepared in similarly looking 50-mL syringes as colourless solutions and handed to the attending anaesthesiologist for administration. The project associates unaware of the group allocation will perform follow-ups of the patients for data collection and assessments. Thus, patients, anaesthesiologists, outcome assessors, and data analysts will remain blinded to study interventions.

We will use a uniform case record form (CRF) for all the centres to collect study data. Baseline details of diagnosis, pre-operative treatment, radiological findings, neurological status, and demographic variables of age, body mass index, and gender will be collected before the surgery.

After establishing standard American Society of Anesthesiologists monitoring, anaesthetic induction will be performed using intravenous (IV) propofol 2 mg/kg or thiopentone 5 mg/kg and lignocaine 1.5 mg/kg. Tracheal intubation will be done after neuromuscular blockade with a non-depolarising muscle relaxant. All patients will receive IV fentanyl 1.5–2 μg/kg, and a minimum alveolar concentration of sevoflurane will be maintained at 0.8–1 to attenuate haemodynamic response before laryngoscopy. Patients in this trial will receive either fentanyl 1 μg/kg/h or dexmedetomidine 0.5 μg/kg/h as a continuous infusion (without bolus dose) during the surgery starting immediately after anaesthetic induction till approximately 30 min before anticipated extubation (corresponding to approximately beginning of skin closure) as the main analgesic according to the randomisation. Reasons for stopping the study drug, if done, will be noted. Anaesthesia will be maintained using air/oxygen/sevoflurane titrated to anaesthetic depth between 40 and 60 on a depth of anaesthesia monitor. Where intra-operative neuromonitoring is planned, anaesthesia will be maintained with IV propofol infusion instead of sevoflurane to a similar anaesthetic depth without changing the analgesia protocol. The attending anaesthesiologist will perform circumferential scalp block using 20 mL of 1% lignocaine with 1:200000 adrenaline and 0.25% bupivacaine to block nerve supply to the scalp before skull clamp fixation. An increase in mean blood pressure or heart rate by more than 30% of baseline value despite adequate anaesthetic depth during surgery will be considered a nociceptive response and treated by administering a bolus of IV fentanyl (1 μg/kg). The total dose of IV fentanyl given in the intra-operative period will be documented. The intravascular volume will be continuously monitored and maintained using fluid administration, and blood loss will be suitably replaced. Approximately 30–60 min before the end of the surgery, all patients will receive IV paracetamol (1 g), ondansetron (4 mg), dexamethasone (8 mg), and either phenytoin (100 mg) or levetiracetam (500 mg) as per institutional policy. After surgery, the incision site will be infiltrated with 0.125% bupivacaine for post-operative pain relief.

We will collect data regarding surgery, dose of intra-operative IV fentanyl (bolus and infusion separately) and dexmedetomidine administered, and pain scores at 15 and 60 min in the post-anaesthesia care unit (PACU) and on the first and second day after surgery by using a numerical rating scale (NRS). We will collect data regarding heart rate, blood pressure, and values of depth of anaesthesia and minimum alveolar concentration of anaesthetic agent in the CRF every 15 min from the beginning of anaesthesia till the extubation.

The primary outcome measures will be a] rescue opioid (IV fentanyl) consumption during surgery and b] post-operative pain using NRS score in the PACU. Our secondary outcome measures will include the following parameters: 1] post-operative pain on first and second post-operative days; 2] adverse events associated with study drugs: incidence of peri-operative hypo- or hypertension, brady- or tachycardia, arrhythmia, PONV, shivering, low respiratory rate, and itching; 3] quality of recovery from anaesthesia and emergence delirium; 4] patient satisfaction assessed at 24 h after surgery by using Likert scale; 5] quality of sleep assessed on first post-operative day by using Likert sleep scale; and 6] persistent pain and quality of life at 3 and 6 months after surgery evaluated telephonically. Figure 2 shows the outcome parameters of the study with corresponding time points of assessments.

Quality of recovery from anaesthesia will be assessed using 1] time to extubation, 2] time to respond to verbal commands from cessation of anaesthesia, 3] coughing (grade 0 = absent cough; grade 1 = mild single cough; grade 2 = moderate cough for <5 s; grade 3 = severe, incessant cough (bucking) for >5 s), 4] blood pressure and heart rate during extubation, and 5] sedation or emergence delirium at 15 and 60 min in the PACU by using Riker sedation agitation scale (SAS) (score 1–7). Heart rate and blood pressure will also be collected in the PACU at 15 and 60 min.

Post-operative pain will be assessed using an NRS score (0–10) after 15 and 60 min of surgery in the PACU. We will assess average and maximum pain in the first 24 and 48 h after surgery. Our post-operative analgesia protocol will be round-the-clock fixed-dose IV paracetamol (15 mg/kg) or diclofenac (1 mg/kg) as per institute protocol and IV tramadol (2 mg/kg) for rescue analgesia if NRS persists >3. Total drugs and dose administered will be recorded.

We will also record the side-effects of hypo- or hypertension, brady- or tachycardia, PONV, post-operative respiratory depression (hypoventilation), itching, shivering, and abnormal recovery from anaesthesia (emergence delirium, delayed recovery, and coughing).

Cardiovascular complications such as brady- or tachycardia and hypo- or hypertension in the peri-operative period will be defined as a 30% change from baseline. After excluding and treating specific causes, persistent manifestations will be symptomatically treated using IV atropine (0.6 mg) or glycopyrrolate (0.2 mg) for bradycardia, esmolol 0.5 mg/kg boluses for tachycardia, labetalol 5 mg boluses for hypertension, and mephentermine 6 mg boluses for hypotension. Post-operative shivering will be classified as 0 = absent shivering, 1 = piloerection without visible muscle activity, 2 = twitches in one muscle group, 3 = twitching of more than one muscle group, and 4 = movements of the entire body.[13] Tramadol (1 mg/kg) and active forced air warming at 40°C will be used to manage shivering when the score is >2. The PONV will be graded as a score of 0–3: 0 = absent PONV, 1 = only nausea,

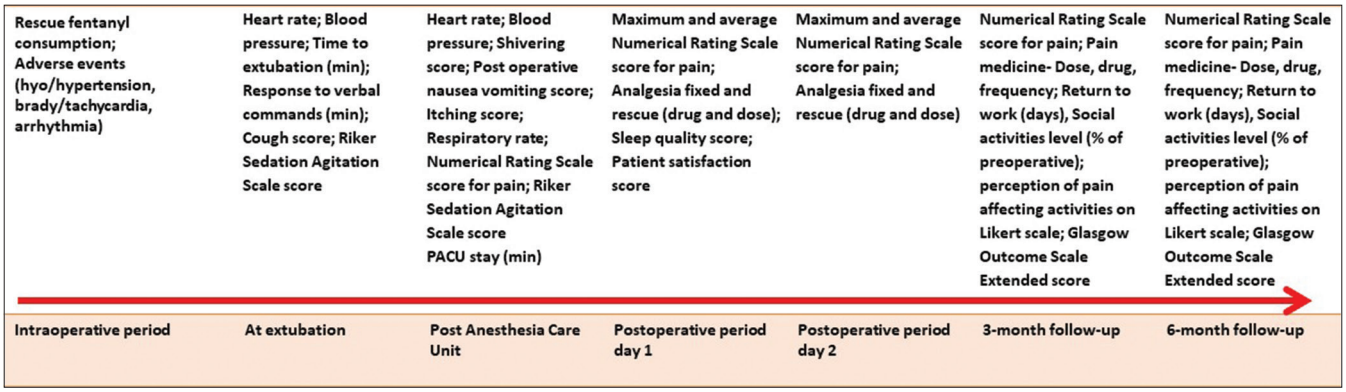

Figure 2: Study outcome parameters with corresponding time points of assessments

2 = vomiting, and 3 = multiple episodes of vomiting, and ondansetron (4 mg) will be given for a score of > 1.[14] Itching will be assessed using NRS (0–10) with 0 = absent and 10 = extreme, with NRS > 3 treated with pheniramine (22.75 mg). Hypoventilation will be considered if the respiratory rate is below 8/min. In such scenarios, end-tidal carbon dioxide ($EtCO_2$) will be assessed to determine the need for elective ventilation ($EtCO_2$ >45 mmHg for >5 min).

Our sample size is calculated based on the difference in pain (NRS score) at 60 min after surgery between dexmedetomidine and fentanyl groups in our pilot study.[11] Considering a power of 80%, a two-sided confidence interval of 95%, and a ratio of sample size of 1, we will need 223 patients per group (total of 446) to detect a significant difference between the two groups. We expect a maximum of 10% (n = 45) data loss for our primary outcome of post-operative pain 60 min after surgery due to non-extubation and no loss for intra-operative opioid consumption outcome. Considering this, we plan to recruit 500 patients (250 in each group) with 100 patients (50/group) enrolled at each of the five participating centres. The first 18 months will be used for patient recruitment, and the remaining 6 months for follow-up. The data will be collected manually by outcome assessors (project associates after intensive training before first patient enrolment) using a standard CRF (proforma) at all the centres. This will then be entered remotely in a Microsoft Excel sheet and stored in a password-protected dedicated Google drive at each centre. The trial status will be reviewed periodically by the project team. The CRF and patient consent forms will be stored safely. The CRF/datasheet will be available to the Data and Safety Monitoring Board (DSMB) for periodic review to ensure the study patients' safety and the collected data's validity and integrity. Any serious adverse events (SAEs) will be promptly documented and reported to the IEC. Any claims arising from the study participants will be brought to the attention of the IEC and the trial insurer. The institute project section will periodically review the progress of the project. Utilisation certificate, statement of expenditure, and annual progress report will be submitted to the funding agency, and an institute auditor will perform the audit at the end of the project.

We will use an intention-to-treat method for data analysis of our outcomes. Data normality will be assessed using the Shapiro–Wilk test. If the distribution is normal, data will be reported as mean and standard deviation (SD); if not, as median and interquartile range (IQR). Appropriate parametric or non-parametric tests will be used. The categorical parameters will be reported as numbers and percentages and analysed using Chi-square or Fischer's exact test. The continuous variables will be analysed using the "t" test. A *P* value of 0.05 will be our threshold for statistical significance. The data will be analysed using the latest version of the statistical package for social sciences or R software.

We do not anticipate multiplicity errors as we do not have multiple sub-groups, multiple treatment arms, or interim analyses at different time points. In addition, we have inflated the sample size to account for any loss and will treat all secondary outcomes as exploratory results. We will analyse primary pain outcomes only in the PACU (and treat pain assessments at other time points as secondary outcomes) to reduce the multiplicity errors arising from pain assessment at multiple time points. For outcomes such as heart rate and blood pressure, where measurements are repeated over time, we will use repeated measures analysis of variance or mixed-effect model for analysis.

RESULTS

We describe the study protocol of our multi-centre trial – protocol version 2, dated 29/01/2022. The first patient was recruited on 19/10/2022, and we expect to complete the patient recruitment before March 2024. Figure 3 summarises the enrolment, intervention, and assessment schedule in the NOPAIN trial as per the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT 2013) recommendations.

DISCUSSION

Our proposed work will likely clarify the benefits of non-opioid dexmedetomidine vis-à-vis opioid analgesia in neurosurgical patients. We expect dexmedetomidine as an alternative to fentanyl will minimise intra-operative opioid usage and improve early post-operative patient outcomes such as pain, sleep, and emergence delirium.

Only a few studies have compared opioids with non-opioids for peri-operative analgesia in patients undergoing craniotomies. Small sample size, single institutional biases, and limited study outcomes significantly limit these studies. Moreover, we have not observed a change in analgesia practice despite non-opioid analgesia being equivalent or

	Time point	Enrolment (-T1)	Allocation (T0)	Intraoperative period (T1)	Extubation (T2)	PACU (T3)	Postoperative day 1 (T4)	Postoperative day 2 (T5)	3-month follow-up (T6)	6-month follow-up (T7)
ENROLMENT	Eligibility screen	X								
ENROLMENT	Informed consent	X								
ENROLMENT	Allocation		X							
INTERVENTIONS	Fentanyl			X						
INTERVENTIONS	Dexmedetomidine			X						
INTERVENTIONS	Rescue opioid consumption			X						
ASSESSMENTS	Postoperative pain, medicines					X	X	X	X	X
ASSESSMENTS	Hemodynamics			X	X	X				
ASSESSMENTS	Adverse events			X	X	X				
ASSESSMENTS	Recovery profile				X	X				
ASSESSMENTS	Sleep and satisfaction						X			
ASSESSMENTS	Neuro outcome, return to activity								X	X

Figure 3: Summary of the schedule of enrolment, intervention, and assessments as per standard protocol items: Recommendations for interventional trials (SPIRIT)

better in these small studies. The novelty of this study is the multi-centre nature, which enhances generalisability and acceptance of results, facilitates faster recruitment, and reduces bias; large sample size, which reduces the margin of error and increases precision; and assessments of other peri-operative outcomes such as sleep, satisfaction, and long-term outcomes of persistent pain and quality of life, apart from opioid requirement and post-operative pain score, which other studies have not evaluated but are essential from patient perspectives. If our research finding demonstrates the significant benefits of dexmedetomidine over fentanyl analgesia, it will likely give clinicians confidence to adopt non-opioids instead of opioids for peri-operative pain management in their routine practice. It will also facilitate the use of dexmedetomidine for pain management in other settings, such as trauma and where opioids are contraindicated, and help provide quality pain relief for every patient undergoing neurosurgery without the fear of opioid side effects, abuse, and narcotic licensing barriers as seen in low-resource settings.

CONCLUSION

The proposed research project's data will enable clinicians to make prudent choices regarding peri-operative analgesia for neurosurgical patients. The proposed non-opioid peri-operative analgesia protocol is simple, cost-effective, non-addictive, and easy to administer as an alternative to opioids to manage intra-operative nociception and post-operative pain.

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Conflicts of interest

There are no conflicts of interest.

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