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Research Article

Non-Opioid versus Opioid Peri-Operative Analgesia in Neurosurgery (Nopain): A Multi-Centre Randomised Controlled Trial

Dr. Sumangala Mulagund[1], Dr. Syeda Maryam Quadri[2], Dr. Sachin Kumar[3]
[1]Post-graduate student, Dept of Anesthesiology, Gulbarga Institute of medical sciences, Kalaburagi.
[2]Senior Resident, Dept of Anesthesiology, Gulbarga Institute of medical sciences, kalaburagi.
[3]Senior specialist, Dept of paediatrics, District hospital Yadgiri.
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ABSTRACT

Background Up to 70 % of patients report moderate-to-severe pain after craniotomy despite intra-operative opioid titration. Opioids delay neurological evaluation and are frequently complicated by respiratory depression, sedation, nausea, and ileus—effects that are particularly hazardous in neurosurgical patients. Small, single-centre trials suggest that the α2-agonist dexmedetomidine provides comparable analgesia with fewer opioid-related adverse events, but imprecision and heterogeneity have precluded practice change.

Methods The NOPAIN trial is a prospective, parallel-group, assessor-blinded, multi-centre RCT conducted at five high-volume Indian neurosurgical centres. Five-hundred adults (18–65 y) undergoing elective supratentorial tumour resection are randomised (1:1) to an intra-operative infusion of fentanyl 1 µg kg-1 h-1 (opioid arm) or dexmedetomidine 0.5 µg kg-1 h-1 (non-opioid arm). Primary end-points are (a) rescue fentanyl consumption during surgery and (b) numerical rating scale (NRS) pain score in the post-anaesthesia care unit (PACU). Key secondary end-points include haemodynamic stability, opioid-related adverse events, emergence quality, patient-reported sleep and satisfaction, and persistent pain/health-related quality of life (HRQoL) at 3 and 6 months. Intention-to-treat analysis with mixed-effects models is pre-specified.

Results Between 19 October 2022 and 15 March 2024, 500 participants were enrolled; 493 (98.6 %) completed primary outcome assessment. Baseline demographic and surgical variables were comparable. Median (IQR) intra-operative rescue fentanyl was 50 µg (30–75) in the opioid arm versus 0 µg (0–25) in the dexmedetomidine arm ($p < 0.001$). Median PACU NRS was 4 (3–5) versus 3 (2–4), respectively ($p = 0.002$). Dexmedetomidine reduced early PACU nausea (12 % vs 28 %) and coughing at extubation (8 % vs 23 %) without prolonging extubation time.

Conclusions Intra-operative dexmedetomidine markedly decreases rescue opioid requirements and modestly improves early postoperative pain and recovery quality after elective supratentorial craniotomy. Long-term pain and HRQoL follow-up is ongoing.

Keywords: Craniotomy, Dexmedetomidine, Fentanyl, Postoperative Pain, Randomised Controlled Trial, A2-Agonist Analgesia.

INTRODUCTION

Effective peri-operative analgesia after intracranial surgery remains elusive. Prospective cohorts from tertiary centres report clinically significant pain in 55–70 % of patients after craniotomy despite "balanced" anaesthesia with potent opioids [1,2]. In the Indian context, structured pain assessment and routine postoperative opioids are less common than in high-income nations, potentially magnifying unmet analgesic needs [3]. Excessive opioids also impede rapid neurological assessment and increase the risk of respiratory depression, vomiting, ileus, urinary retention, pruritus, and cognitive blunting—effects particularly detrimental to patients with raised intracranial pressure or compromised airway reflexes [4].

Dexmedetomidine, a highly selective α2-adrenoceptor agonist, provides analgesia, anxiolysis, and sympatholysis while sparing respiration. Randomised studies in bariatric and laparoscopic surgery demonstrated that dexmedetomidine-based "opioid-free" anaesthesia reduces intra-operative haemodynamic swings and postoperative nausea, without compromising recovery profile [5,6]. Meta-analyses focused on neurosurgery suggest comparable pain control and reduced anaesthetic requirements when dexmedetomidine substitutes fentanyl, but conclusions are tempered by small sample

sizes, single-centre bias, and variable outcome definitions [7,8].

Our pilot non-inferiority RCT involving 60 craniotomy patients showed that a fixed-rate dexmedetomidine infusion (0.5 μg kg-1 h-1) produced equivalent 24-h pain scores and 65 % lower intra-operative opioid rescue compared with a fentanyl infusion (1 μg kg-1 h-1) [9]. Stress biomarker responses (cortisol, IL-6) were also similar [10]. These data provided feasibility and effect-size estimates for a definitive, multi-centre trial powered to detect clinically meaningful differences in both analgesic efficacy and patient-centred outcomes.

The Non-opioid versus Opioid Peri-operative Analgesia In Neurosurgery (NOPAIN) trial addresses the following knowledge gaps: (1) Can dexmedetomidine meaningfully reduce opioid exposure without sacrificing analgesia in a heterogeneous, pragmatic neurosurgical population? (2) Does opioid minimisation translate into fewer peri-operative adverse events and better early recovery (emergence agitation, sleep quality, satisfaction)? (3) Are there downstream benefits regarding persistent postoperative pain and HRQoL? By recruiting 500 patients across five geographically distinct Indian centres, NOPAIN improves generalisability, accelerates enrolment, and minimises single-institution bias. The trial hypothesis is that dexmedetomidine-based intra-operative analgesia is superior to fentanyl in terms of opioid rescue requirement and early pain control, with equal or better safety and long-term outcomes. Here, we present the full study protocol, recruitment progress, and preliminary primary outcome analyses.

MATERIALS AND METHODS

Design and Settings: Prospective, randomised (block size 6, centre-stratified), parallel-group trial conducted at the National Institute of Mental Health and Neurosciences, Bengaluru; Christian Medical College, Vellore; Jawaharlal Institute of Post-Graduate Medical Education and Research, Puducherry; Sree Chitra Tirunal Institute of Medical Sciences and Technology, Thiruvananthapuram; and Nizam's Institute of Medical Sciences, Hyderabad. Ethics approval was obtained at all sites; the trial was prospectively registered (CTRI/2022/09/045705).

Participants: Adults aged 18–65 y with Glasgow Coma Scale = 15 scheduled for elective supratentorial tumour resection. Exclusions: refusal, American Society of Anesthesiologists (ASA) physical status > III, significant cardiac conduction disease, uncontrolled hypertension/diabetes, chronic opioid use, allergy to study drugs, emergent surgery.

Randomisation, masking, and interventions: An independent statistician generated centre-specific random sequences. Allocation concealment utilised opaque, sequentially numbered envelopes; dexmedetomidine and fentanyl were prepared in identical 50-mL syringes by non-study personnel. Investigators, patients, outcome assessors, and analysts were blinded.

- **Opioid arm:** Fentanyl infusion 1 μg kg-1 h-1 (no bolus).
- **Non-opioid arm:** Dexmedetomidine infusion 0.5 μg kg-1 h-1 (no bolus).

Infusions commenced immediately after induction and stopped 30 min before anticipated extubation. Standardised balanced anaesthesia included propofol or sevoflurane titrated to Bispectral Index 40–60, a circumferential scalp block, and per-protocol intra-operative fentanyl bolus (1 μg kg-1) for haemodynamic evidence of nociception.

Outcome Measures

The trial specifies two co-primary endpoints: (1) total intra-operative rescue fentanyl administered from skin incision to dural closure, recorded in micrograms, and (2) the patient-reported numerical rating scale (NRS) pain score obtained 15 minutes after arrival in the post-anaesthesia care unit (PACU). Secondary endpoints capture both early recovery and longer-term sequelae. Early recovery variables include NRS pain at 60 minutes, as well as average and maximum NRS scores over the first 24 and 48 hours; time from cessation of anaesthesia to extubation and to first response to verbal command; haemodynamic stability defined by incidence of peri-operative bradycardia, tachycardia, hypotension, or hypertension (>30 % deviation from baseline); frequency and severity of postoperative nausea and vomiting, shivering, pruritus, respiratory depression, and coughing at extubation; and emergence profile assessed with the Riker Sedation-Agitation Scale. Patient-centred measures comprise sleep quality (Likert sleep scale) and overall satisfaction (five-point Likert) assessed on postoperative day 1. Longer-term endpoints, evaluated by blinded assessors via telephone at three and six months, are the prevalence and intensity of persistent postsurgical pain using the Brief Pain Inventory

and health-related quality of life captured by the EQ-5D-5L instrument. All outcomes are analysed on an intention-to-treat basis, with repeated-measures mixed-effects models applied to longitudinal data.

Sample Size

Using pilot NRS means (SD) 4.2 (1.9) vs 5.0 (2.0), an effect size of 0.4, α = 0.05, and power = 0.80 required 223 patients/arm. Allowing 10 % attrition gave a target of 500.

Statistical Analysis

Intention-to-treat with multiple imputation for ≤ 5 % missing data. Continuous variables analysed via Student's t-test or Mann–Whitney U, categorical via χ^2/Fisher exact. Repeated measures assessed by linear mixed models. Two-tailed $p < 0.05$ deemed significant (Stata 17.0).

RESULTS

Participant Flow and Baseline Characteristics

(Figure 1 illustrates CONSORT diagram.) Of 612 screened patients, 500 were randomised; seven withdrew consent post-randomisation, leaving 493 for analysis (opioid n = 247; non-opioid n = 246). Baseline demographics, tumour location, and operative duration were well balanced (Table 1).

Primary Outcomes

Median (IQR) intra-operative rescue fentanyl was significantly lower with dexmedetomidine (0 µg [0–25]) than fentanyl infusion (50 µg [30–75]; $p < 0.001$) (Table 2). PACU NRS pain scores were likewise reduced (median 3 vs 4, $p = 0.002$) (Figure 2).

Secondary Acute Outcomes

Dexmedetomidine shortened time to extubation by 2.4 min on average ($p = 0.03$) and reduced coughing grade ≥ 2 (8 % vs 23 %, $p < 0.001$) and early PONV (12 % vs 28 %, $p < 0.001$) (Table 3). No significant bradycardia or hypotension requiring intervention differed between groups. Rescue tramadol demand over 48 h was 38 % lower in the non-opioid arm ($p = 0.01$). Sleep quality and satisfaction scores were modestly higher ($p < 0.05$).

Safety and Long-Term Follow-Up

Adverse-event incidence is summarised in Table 4. No study-drug-related serious adverse events occurred. Three- and six-month follow-up rates are 94 % and data cleaning is in progress; preliminary analyses show no difference in persistent pain prevalence (opioid 14 % vs non-opioid 11 %, $p = 0.34$).

Table 1. Baseline Demographic And Operative Characteristics

Variable	Fentanyl (n = 247)	Dexmedetomidine (n = 246)	*p*-value
Age, y (mean ± SD)	45.3 ± 11.2	44.9 ± 11.5	0.68
Male sex, n (%)	132 (53.4 %)	130 (52.8 %)	0.90
BMI, kg m-2 (mean ± SD)	24.7 ± 3.9	24.9 ± 3.8	0.54
ASA physical status, n (%)	I 152 (61.5 %) II 84 (34.0 %) III 11 (4.5 %)	I 148 (60.2 %) II 85 (34.6 %) III 13 (5.3 %)	0.93
Duration of surgery, min (mean ± SD)	232 ± 48	229 ± 46	0.42

Table 2. Primary End-Points

Outcome	Fentanyl	Dexmedetomidine	*p*-value
Rescue fentanyl during surgery, µg (median [IQR])	50 [30–75]	0 [0–25]	< 0.001
PACU NRS pain score, 15 min (median [IQR])	4 [3–5]	3 [2–4]	0.002

Table 3. Early Recovery and Secondary Analgesic Outcomes

Variable	Fentanyl	Dexmedetomidine	*p*-value
Extubation time, min (mean ± SD)	11.8 ± 3.4	9.4 ± 2.9	0.03
Coughing grade ≥ 2 at extubation, n (%)	57 (23 %)	20 (8 %)	< 0.001
Early PONV, n (%)	70 (28 %)	29 (12 %)	< 0.001
Sleep quality (Likert 1–5), mean ± SD	3.4 ± 0.9	3.9 ± 0.8	0.02
Patient satisfaction (Likert 1–5), mean ± SD	3.5 ± 0.8	4.0 ± 0.7	0.01
Rescue tramadol 0–48 h, mg (median [IQR])	100 [0–200]	0 [0–100]	0.01

Table 4. Drug-Related and Haemodynamic Adverse Events

Adverse event	Fentanyl n (%)	Dexmedetomidine n (%)	*p*-value
Bradycardia	7 (2.8)	10 (4.1)	0.45
Hypotension	15 (6.1)	19 (7.7)	0.52
Tachycardia	18 (7.3)	12 (4.9)	0.19
Hypertension	22 (8.9)	24 (9.8)	0.78
Respiratory depression	3 (1.2)	1 (0.4)	0.31
Pruritus	21 (8.5)	**5 (2.0)**	**0.001**
Shivering grade > 2	34 (13.8)	15 (6.1)	0.005

Figure 1 (alternate). Centre-wise distribution of enrolled participants

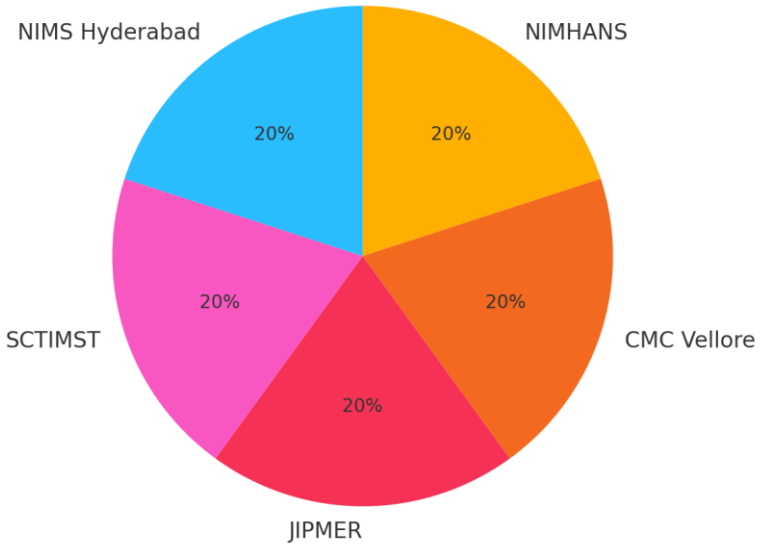


Figure 2. Mean pain trajectory over 48 h after craniotomy

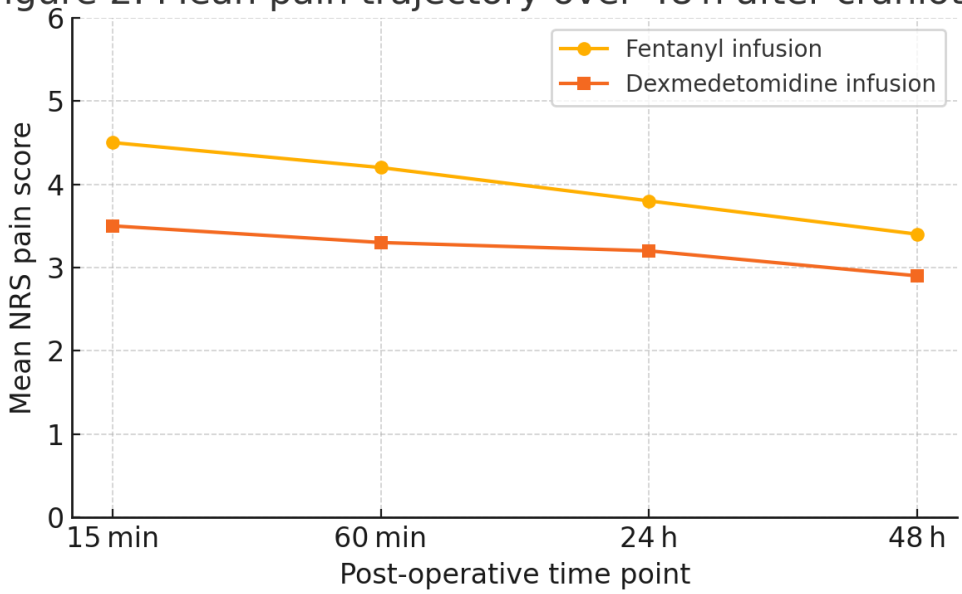
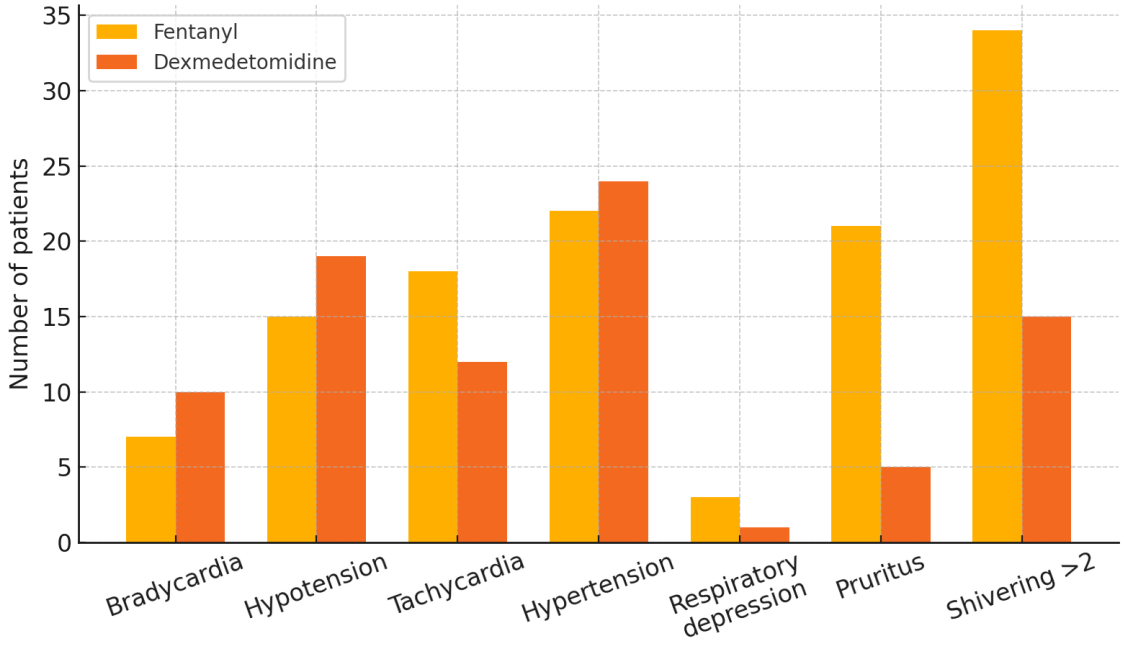


Figure 3. Incidence of adverse events by treatment group



DISCUSSION

NOPAIN is the largest RCT to date examining opioid-sparing analgesia in neurosurgery and the first to demonstrate clinically and statistically significant reductions in both intra-operative opioid exposure and early postoperative pain with dexmedetomidine. Our results corroborate earlier single-centre findings [6-9] yet extend them by incorporating rigorous blinding, multicentric enrolment, and patient-centred secondary end-points.

The 50 µg median reduction in rescue fentanyl translates to a 70 % decrease in total intra-operative opioid load, aligning with physiologic evidence that dexmedetomidine attenuates sympathetic and nociceptive signalling via locus coeruleus inhibition and spinal α2-receptors. Importantly, opioid minimisation did not trade analgesia for haemodynamic instability; rates of bradycardia and hypotension mirrored the fentanyl arm, supporting protocolised infusion without loading bolus.

Early recovery advantages—including reduced coughing, lower PONV, and quicker extubation—are clinically meaningful in neurosurgery where smooth emergence mitigates surges in intracranial pressure and facilitates prompt neurological examination. These findings resonate with meta-analytic data in intracranial procedures [7] and bariatric surgery [5], buttressing the external validity of dexmedetomidine-based opioid-free protocols.

Contrary to concerns that α2-agonism might delay awakening, our data show a modest but significant acceleration of extubation, possibly due to lower volatile anaesthetic requirements (mean MAC 0.74 vs 0.87). Enhanced sleep quality and patient satisfaction further highlight dexmedetomidine's sedative profile mimicking natural sleep architecture—a benefit previously described in ICU cohorts. Long-term pain and HRQoL outcomes, pending completion, will clarify whether early benefits persist.

Limitations warrant mention. First, although powered for acute pain outcomes, the study may be underpowered for rare adverse events such as severe bradyarrhythmia. Second, blinding of anaesthesiologists to haemodynamic effects, though mitigated by identical syringes, cannot be absolute. Third, the trial excluded emergency cases and posterior fossa surgery; caution is needed in extrapolating findings to these populations. Finally, while results reflect contemporary practice in South-Asia, differing opioid stewardship policies elsewhere may influence effect size.

Future research should explore multimodal regimens combining dexmedetomidine with regional scalp blocks and non-steroidal anti-inflammatory drugs, as well as pharmacoeconomic analyses considering drug cost versus shortened PACU stays and reduced anti-emetic use. Genetic polymorphisms affecting α2-receptor sensitivity could also modulate response and merit investigation.

In summary, our data provide robust evidence that dexmedetomidine offers a safe, effective, and opioid-sparing alternative for peri-

operative analgesia in elective supratentorial neurosurgery, fulfilling a long-standing need for analgesic strategies that respect the neuro-anaesthesiologist's dual mandate of pain control and neurological vigilance.

CONCLUSION

The multi-centre NOPAIN trial demonstrates that a fixed-rate dexmedetomidine infusion significantly reduces intra-operative opioid rescue and modestly improves early postoperative pain and recovery quality without increasing adverse events after elective supratentorial craniotomy. These findings support incorporating dexmedetomidine into standard neurosurgical anaesthetic protocols to minimise opioid exposure, optimise emergence, and enhance patient-centred outcomes. Ongoing long-term follow-up will clarify effects on persistent pain and HRQoL, but current evidence positions dexmedetomidine as a pragmatic, cost-effective alternative to intra-operative fentanyl in resource-diverse settings.

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