Assessment and management of perioperative pain in neurosurgical patients

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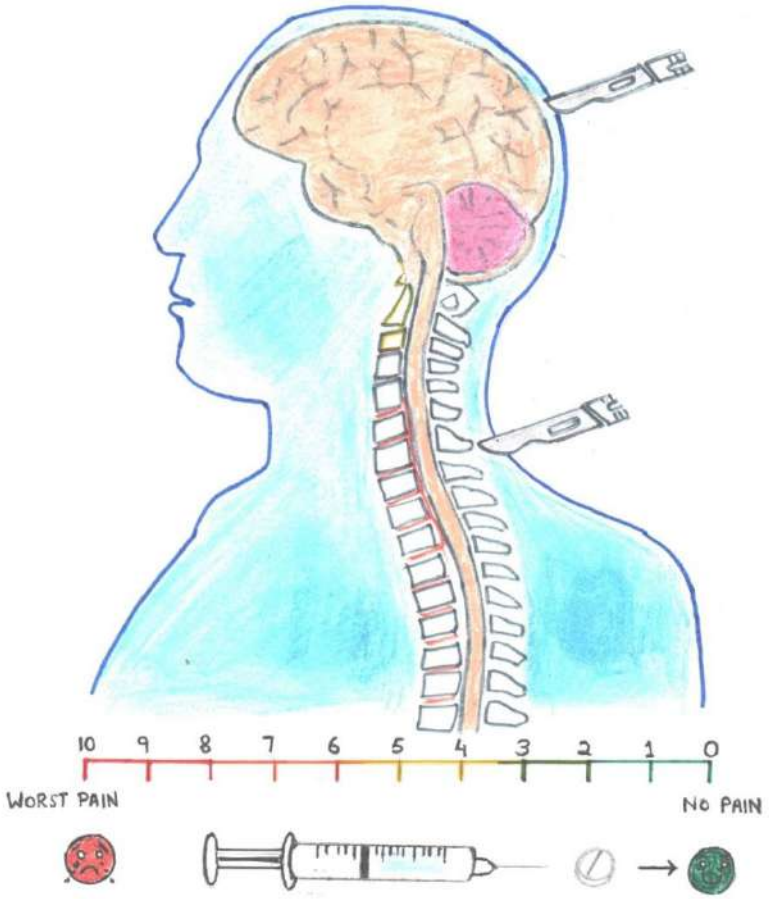

Sriganesh Kamath D.M.,

"Assessment and management of perioperative pain in neurosurgical patients"

Sriganesh Kamath D.M.

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DISSERTATION

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Prof. dr. Pamela Habibović
in accordance with the decision of the Board of Deans,
to be defended in public
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by

Sriganesh Kamath

born on 22nd July 1977
Mulki, India

Supervisors

Prof. dr. Harry W.M. Steinbusch

Prof. dr. T.N. Sathyaprabha, National Institute of Mental Health and Neurosciences, Bengaluru, India

Prof. dr. G.S. Umamaheswara Rao, National Institute of Mental Health and Neurosciences, Bengaluru, India

Assessment Committee

Prof. dr. D.E.J. Linden, CHAIR

Prof. dr. Sethuraman Manikandan, Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Trivandrum, India

Prof. dr. Girija Prasad Rath, All India Institute of Medical Sciences (AIIMS), New Delhi, India

Prof. Dr. H. van Santbrink

Dr. C. Vossen

Dedicated to my Patients, Guides, Teachers, Students,

Friends and Family

Abbreviations

ACTH – Adreno Cortico Trophic Hormone

AIMS - Anesthesia Information Management System

ANI - Analgesia Nociception Index

ANIi – Analgesia Nociception Index Instantaneous

ANIm - Analgesia Nociception Index Mean

ASA - American Society of Anesthesiologists

BMI - Body Mass Index

CI – Confidence Interval

CTRI - Clinical Trial Registry of India

DLTI - Direct Laryngoscopy Tracheal Intubation

GRADE - Grading of Recommendations, Assessment, Development and Evaluations

HBI – Heart Beat Interval

HF – High Frequency

HR – Heart Rate

HRV – Heart Rate Variability

ICU - Intensive Care Unit

IQR – Inter Quartile Range

ISNACC - Indian Society of Neuroanaesthesiology and Critical Care

LC - Leucocyte Count

LF – Low Frequency

MAC - Minimum Alveolar Concentration

MBP – Mean Blood Pressure

MD – Mean Difference

NRS - Numerical Rating Scale

NSAIDs - Non-Steroidal Anti-Inflammatory Drugs

OR - Odds Ratio

PACU - Post-Anesthesia Care Unit

PONV- Post-Operative Nausea and Vomiting

PPWA - Plethysmographic Pulse Wave Amplitude

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO - international prospective register of systematic reviews

RASS - Richmond Agitation Sedation Scale

RBG - Random Blood Glucose

RCT- Randomized Controlled Trial

RMANOVA - Repeated-Measures Analysis of Variance

RoB - Risk of Bias

RR - Risk Ratio

SD - Standard Deviation

SPI – Surgical Pleth Index

SPSS - Statistical Package for Social Sciences

SSI - Surgical Stress Index

TIVA - Total Intra-Venous Anesthesia

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CHAPTER 1

INTRODUCTION

Chapter 1: Introduction

1.1: Brief introduction to perioperative pain and its effect on outcomes

The International Association for the Study of Pain in its recent revision defined pain as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage". [1] Acute postoperative pain is reported by many patients undergoing surgical procedures. [2] The severity and incidence of postoperative pain are dependent on several factors including pre-existing pain, preoperative psychological status, intraoperative anesthesia and analgesia management, the extent of noxious surgical and non-surgical stimuli, monitoring of nociception during surgery, and quality of postoperative analgesia administered. [3-5] Nociception refers to the processing of a noxious stimulus resulting in the perception of pain by the brain. [6]

Acute postoperative pain can result in adverse consequences such as delayed ambulation, dissatisfaction, poor sleep, agitation and delirium, poor respiratory function, cardiovascular activation, delayed discharge from hospital, and also contribute to the occurrence of persistent/chronic post-surgical pain. [7] Therefore, effective pain management in the perioperative period is vital to address this undesirable complication after surgery.

1.2: Assessment of pain during and after surgery under general anesthesia

Pain is a subjective experience, and perception and reporting of pain varies between individuals for similar stimuli depending on several factors such as socio-cultural background, gender, age, education, income, emotional, psychological, and cognitive status, etc. [8] This subjective assessment of pain is not possible when

patients undergo surgeries with general anesthesia. Hence, attempts have been made to explore if an objective assessment of nociception during surgery is feasible using a variety of surrogate tools. These methods are also correlated with postoperative patient-reported pain scores. The changes in heart rate and blood pressure, and patient movement are some of the clinical signs of pain/nociception in the intraoperative period. [9] However, they may not be reliable as these changes can occur due to causes other than pain such as blood loss or changes in depth of anesthesia. In the recent years, intraoperative assessment of surgical stress/nociception/pain has been possible due to the availability of monitors such as surgical pleth index (SPI) or analgesia nociception index (ANI). [10, 11] These tools also help in assessing adequacy of response to treatment of pain with analgesics. [12]

The SPI evaluates peripheral vasoconstriction and cardiac autonomic tone using heartbeat interval (HBI) and photo-plethysmo-graphic amplitude (PPGA). The SPI ranges from 0 to 100 with values more than 50 indicating nociception. The ANI calculates the area under the curve of the high-frequency spectrum of heart rate variability (HRV) and provides a value between 0 and 100. In contrast to SPI, pain/nociception is likely when the ANI value decreases below 50. Both SPI and ANI have been validated for pain assessment in surgical patients. [10-12]

Postoperative pain can be assessed using different self-reported methods with the most common being - no pain, mild pain, moderate pain and severe pain. The scales used for postoperative pain assessment include visual analog scale (VAS) score, verbal rating scale (VRS) score, numerical rating scale (NRS) score, etc. [6] Most of these scales are represented from 0 to 10 with 0 being no pain and 10 being

the worst pain imaginable. Multi-dimensional pain scales such as McGill Pain Questionnaire, and Brief Pain Inventory not only assess pain intensity but also mood, behavior, thoughts and beliefs, physiological effects, and their interaction. [6] These are not routinely used in the postoperative period due to time factor but provide greater information than uni-dimensional pain scales.

1.3: Management of pain during and after surgery

Patients experience acute surgical pain due to trauma, tissue damage, and inflammation at the operative site. Potent opioids such as morphine, fentanyl, and remifentanil are the primary analgesics used during general anesthesia for surgical procedures. However, due to the problems associated with opioid side effects, non-opioid analgesia is employed during surgery either alone or in combination with opioids to reduce opioid requirements and minimize opioid-related adverse effects. The non-opioid analgesia techniques to reduce postoperative pain include perioperative gabapentinoids, neuraxial blocks such as spinal or epidural anesthesia, local anesthesia infiltration at the incision site or regional nerve blocks with local anesthetics, systemic analgesia with non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, and continuous intravenous infusion of drugs such as dexmedetomidine, lignocaine, ketamine, or magnesium. [13] A combination of these analgesic agents constitutes multi-modal analgesia.

The benefits of intraoperative analgesia often extend into the early postoperative period. Additionally, the above-mentioned drugs also remain part of postoperative analgesia practice. Patient-controlled analgesia is another technique for postoperative pain management where it provides for greater autonomy to the

patients with regards to their pain management. [14] As the postoperative pain is maximal during the initial few days after surgery, pain medications are administered as part of standard care and subsequently on a need basis in many hospitals.

1.4: Pain and neurosurgery

Pain after neurosurgery is reported by up to two-thirds of patients. Though the brain per-se is insensitive to pain, tissue injury involving structures such as muscles, soft tissues of the scalp, and periosteum of the cranial bone may all contribute to pain. Pain is sometimes undertreated in neurosurgical patients due to apprehension of opioid-associated side effects. [15] Moreover, pain assessment may be a challenge in patients undergoing surgery for brain pathologies when they may not be able to report pain accurately due to neurological problems such as altered sensorium or aphasia. Regional analgesia techniques such as scalp nerves block and pin-site and operative site local anesthetic infiltration helps minimize postoperative pain in craniotomy patients. [16-18]

Pain following spine surgery is also a commonly reported outcome. Many patients undergoing spine surgery also have pre-existing pain. The extent of surgical incision determines the severity of pain with minimally invasive spine surgeries having the least postoperative pain. Regional analgesia such as erector spinae plane block [19] or epidural analgesia reduce the need of opioids during surgery and yet provide effective perioperative analgesia. Systemic analgesic infusions of non-opioid drugs also reduce both opioid requirement and postoperative pain. [20]

Aims and Objectives

Aim: The aim of this PhD was to evaluate various assessment methods of perioperative nociception/pain and techniques of intraoperative analgesia for postoperative pain management in neurosurgical patients.

The objectives were:

1. Perioperative pain assessment and management in neurosurgical patients varies widely across the globe. To understand the Indian perspective, we asked the research question - how is pain assessed and managed in neurosurgical patients in India? To answer this question, we conducted a national survey about the practices and perceptions regarding perioperative pain assessment and management in neurosurgical patients among Indian neuroanesthesiologists and evaluated if the hospital and pain characteristics predicted the use of structured pain assessment protocol and use of opioids for postoperative pain management. (chapter 2)
2. Postoperative pain is common after craniotomy; however, its incidence varies across the world. We asked the research question – What are the incidences and predictors of post-craniotomy pain in India? We therefore conducted a prospective observational study to assess the incidence, risk factors and impact of acute postoperative pain after intracranial neurosurgeries. (chapter 3)
3. Tracheal intubation is one of the most noxious stimuli during anesthesia. We asked the research question – Is there a correlation between the conventionally used hemodynamic parameters and a newer nociception

monitor during intubation? To answer this question, we conducted a study comparing the changes in heart rate and blood pressure with the changes in analgesia nociception index during anesthetic induction and tracheal intubation. (chapter 4)

4. Nociception and stress response during surgery may vary between opioid and non-opioid analgesia. We asked a research question – Is the stress response to cranial neurosurgery different between opioid and non-opioid intraoperative analgesia techniques? We therefore conducted a study comparing surgical stress response using blood biomarkers and surgical pleth index in patients receiving opioids and non-opioids for analgesia during craniotomy. (chapter 5)
5. Small studies have shown variable results for postoperative pain outcomes with intraoperative opioid and non-opioid analgesia. We asked the research question – Is a large randomized controlled trial (RCT) comparing opioid and non-opioid intraoperative analgesia feasible and is non-opioid analgesia non-inferior to opioid analgesia in patients undergoing craniotomy? To answer these questions, we conducted a RCT comparing fentanyl with dexmedetomidine for perioperative analgesia during craniotomy. (chapter 6)
6. Previous RCTs comparing intraoperative opioids with non-opioid analgesia for postoperative pain involved a small number of patients and reported conflicting findings. We asked a research question – What is the overall pooled effect for post-craniotomy pain outcomes from RCTs comparing intraoperative opioids with non-opioid analgesia? We therefore conducted a

systematic review and meta-analysis of RCTs comparing opioid and non-opioid analgesia during craniotomies with regards to postoperative pain outcomes. (chapter 7)

7. We asked a similar question for patients undergoing spine surgeries – What is the cumulative evidence synthesized from RCTs comparing opioid and non-opioid analgesia for postoperative pain after spine surgeries? To answer this research question, we performed a systematic review and meta-analysis of RCTs evaluating intraoperative opioids with non-opioids with regards to postoperative pain and adverse outcomes in spine surgery population. (chapter 8)

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CHAPTER 2

PERIOPERATIVE ANALGESIA IN NEUROSURGERY (PAIN): A NATIONAL SURVEY OF PAIN ASSESSMENT AND MANAGEMENT AMONG NEUROANESTHESIOLOGISTS OF INDIA

Sriganesh K, Bidkar P, Krishnakumar M, Singh GP, Hrishi AP, Jangra K.

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Perioperative Analgesia in Neurosurgery (PAIN): A national survey of pain assessment and management among neuroanesthesiologists of India

Kamath Sriganesh[1] | Prasanna Udupi Bidkar[2] | Mathangi Krishnakumar[1] | Gyaninder Pal Singh[3] | Ajay Prasad Hrishi[4] | Kiran Jangra[5]

[1]National Institute of Mental Health and Neuro Sciences, Bangalore, India

[2]Jawaharlal Institute of Post Graduate Medical Education and Research, Pondicherry, India

[3]All India Institute of Medical Sciences, New Delhi, India

[4]Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, India

[5]Post Graduate Institute of Medical Education and Research, Chandigarh, India

Correspondence
Kamath Sriganesh, National Institute of Mental Health and Neuro Sciences, Bangalore, India.
Email: drsri23@gmail.com

Abstract

Background: Perioperative pain assessment and management in neurosurgical patients varies widely across the globe. There is lack of data from developing world regarding practices of pain assessment and management in neurosurgical population. This survey aimed to capture practices and perceptions regarding perioperative pain assessment and management in neurosurgical patients among anesthesiologists who are members of the Indian Society of Neuroanaesthesiology and Critical Care (ISNACC) and evaluated if hospital and pain characteristics predicted the use of structured pain assessment protocol and use of opioids for postoperative pain management.

Methods: A 26-item English language questionnaire was administered to members of ISNACC using Kwiksurveys platform after ethics committee approval. Our outcome measures were adoption of structured protocol for pain assessment and opioid usage for postoperative pain management.

Results: The response rate for our survey was 55.15% (289/524). One hundred eighteen (41%) responders informed that their hospital setup had a structured pain protocol while 43 (15%) responders reported using opioids for postoperative pain management. Predictors of the use of structured pain protocol were private setup (odds ratio [OR] 2.64; 95% confidence interval [CI] 1.52-4.59; $P = .001$), higher pain intensity (OR 0.37; 95% CI 0.21-0.64; $P < .001$) and use of pain scale (OR 7.94; 95% CI 3.99-15.81; $P < .001$) while availability of structured pain protocol (OR 2.04; 95% CI 1.02-4.05; $P = .043$) was the only significant variable for postoperative opioid use.

Conclusions: Less than half of the Indian neuroanesthesiologists who are members of ISNACC use structured protocol for pain assessment and very few use opioids for postoperative pain management in neurosurgical patients.

1 | INTRODUCTION

Perioperative pain management is an important component of anaesthesia care for neurosurgical patients. However, the practice of perioperative pain assessment and management varies widely between different countries and also within the country. Absence of protocolised pain assessment and management is one of the reasons for differences in perioperative pain management by clinicians in

various hospitals. There is some prior knowledge about pain management practices after neurosurgery from the developed world such as Canada,[1] United Kingdom[2-4] and Korea.[5] However, such data are lacking among low- and middle-income countries which cater to more than 80% of world's neurosurgical volume.[6] India, with over 1.37 billion people, is home to about 18% of the world's population[7] and despite thousands of neurosurgical procedures being performed annually, there is no national data regarding how perioperative pain is managed in this population.

To overcome this knowledge gap regarding perioperative pain assessment and management practices in neurosurgical patients in India, this survey was conducted. The objective of this survey was to capture preferences, practices and perceptions regarding perioperative pain assessment and management in neurosurgical patients among Indian neuroanesthesiologists. We also aimed to evaluate if any hospital and pain characteristics predicted adoption of structured pain assessment protocol and use of opioids for postoperative pain management.

What's known

- Perioperative pain assessment and management vary widely across the globe.
- Adoption of structured pain protocols and use of opioids for postoperative pain management is common in developed nations.
- There is inadequate data regarding pain management practices in the developing world.

What's new

- This survey informs practices and perceptions regarding perioperative pain assessment and management in neurosurgical patients among Indian anesthesiologists.
- Less than half of the Indian neuroanesthesiologists who are members of ISNACC use structured protocol for pain assessment and only few use opioids for postoperative pain management in neurosurgical patients.

2 | MATERIALS AND METHODS

The study design was a cross-sectional survey. The National Institute of Mental Health and Neurosciences ethics committee (Basic and Neurosciences) accorded expedited approval for this survey on 29 July, 2019. We developed a 26-item English language questionnaire to evaluate practices, preferences and perceptions regarding perioperative pain assessment and management among anesthesiologists providing services for neurosurgical patients. The questionnaire was pretested among six anesthesiologists with experience and interest in perioperative pain in neurosurgical population. Their feedback was used to improve relevance, clarity and appropriateness of questions and responses. The final questionnaire was a closed-ended response options as a previous report has shown this to be superior to open-ended format with regard to completeness of responses.[8]

We used Kwiksurveys (https://kwiksurveys.com) platform to design and administer our anonymous questionnaire to members of the Indian Society of Neuroanaesthesiology and Critical Care (ISNACC), the official society of the neuroanesthesiologists of India, whose members predominantly provide perioperative services for neurosurgical patients in the country. The participants were informed that the completion of the survey implied their consent for participation in the survey and for sharing of anonymised data with the scientific community. The initial seven questions pertained to the demographic details of the responders and the rest 19 questions were about assessment and management of perioperative pain in neurosurgical patients.

The database of members of ISNACC was obtained on 15-07-2019 and had 585 names listed as members with their email and/or phone details. The link to the survey website along with a brief introduction to our survey was communicated by email to these members. The email was not successfully delivered to 56 persons as either the email address could not be found or the person was unable to receive the email. Thus, 529 persons received our email with link to the questionnaire. Three informed that they did not practice neuroanesthesia anymore and two informed that they were neurosurgeons and therefore did not wish to participate. After excluding these, survey was shared with 524 members every week (by email and via a closed group social media platform of members) for 3 consecutive weeks to facilitate participation in the survey and enhance the number of responses. Only those who did not respond to the survey initially were requested to complete the survey during the subsequent reminders to avoid respondents from completing the survey more than once. We, however, could not specifically identify and exclude from the database those who had retired from practice or had expired.

We wanted to find out if there is any difference in adoption of structured pain protocol between (a) academic hospital and non-academic hospital, (b) private and government work setup (c) hospital with >500 beds and ≤500 beds, (d) assessors believing that most patients develop moderate-to-severe pain and those believing that most patients develop no or mild postoperative pain, (e) pain assessment by doctors and non-doctors, (f) those using pain scales (visual analogue scale or numerical rating scale) and no scales (no formal assessment or yes/no or no/mild/moderate/severe) and (g) those using opioids and not using opioids for postoperative pain management. A written hospital document informing how pain is assessed and managed after surgery constituted a structured pain protocol/format.

We also wanted to find out if opioid analgesics are more likely to be used for postoperative pain management (a) in academic hospitals, (b) in private hospitals (c) in hospitals with >500 beds, (d) when co-analgesics are not used in the perioperative period, (e) when loco-regional analgesia is not used during surgery and 6] where structured pain protocol is exists.

2.1 | Statistical analyses

Statistical analyses were performed using Statistical Packaging for Social Sciences version 16 (SPSS Inc, Chicago, IL). We report variables in terms of frequencies and percentages. Categorical data were analysed by chi-square test or Fisher's exact test. We performed binary logistic regression analysis to assess factors associated with our binary-dependent outcomes. Factors significantly associated ($P < .2$) with outcomes on univariable regression analyses were used for performing multivariable analyses. A $P < .05$ was considered to be statistically significant for multivariable analyses. For the purpose of analyses, we collapsed independent variables with <40 observations with other related variables and excluded individual variables when this was not possible. We did this to provide some reassurance that each variable has sufficient discriminant power to detect an association with structured format/protocol for pain assessment and management, and postoperative opioid analgesia, if such an association existed. We report odds ratios (ORs) and 95% confidence intervals (CIs) for the variables in our final model. Goodness of fit for the multivariable regression model was determined by the Hosmer-Lemeshow test which measures the predictive reliability by comparing expected with actual results of the dependent variable.[9]

2.2 | Sample size estimation

Considering a margin of error of 5% and a confidence level of 95%, the number of completed surveys required was determined to be 233 for our target population of ISNACC members of 585. The response rate for our earlier survey in the same population was noted to be 32%.[10] This time, in addition to the email communication with link to the survey, we planned to utilize social media platform of ISNACC and influence of ISNACC leaders to enhance members' participation in our survey. Sharing the survey link through ISNACC official WhatsApp group enabled participation of those who could not receive the link due to changed email or email reaching spam or junk box. ISNACC leaders are well known and more influential than ordinary members within our neuroanesthesia community and therefore their personal intervention would yield more completed responses. With these interventions, we aimed to achieve a response rate of atleast 50% for this survey.

3 | RESULTS

The overall response rate for our survey was 55.34% (290/524). The demographic details of the anesthesiologists who responded to our survey are shown in Table 1. The details regarding assessment and management of perioperative pain in neurosurgical patients is shown in Appendix S1. Regarding our outcomes, 118 (41%) responders informed that their hospital setup had a structured protocol for assessment and management of postoperative pain while only 43 (15%) responders reported using opioids for postoperative pain management in neurosurgical patients.

TABLE 1 Demographic details of the responders (n = 290)

Characteristic assessed	N (%) of responders
Male gender	172 (60)
Current work location	
North India	103 (36)
South India	112 (39)
East India	22 (8)
West India	37 (13)
Central India	7 (2)
Outside India	8 (3)
Workplace setting	
Freelance	3 (1)
Academic Government	144 (50)
Non-Academic Government	4 (1)
Academic Private	102 (36)
Non-Academic Private	33 (12)
Hospital bed strength	
<100	15 (5)
101-500	102 (36)
501-1000	68 (24)
>1000	101 (35)
Postqualification experience in anaesthesia (y)	
<5	63 (22)
5-10	89 (31)
11-20	90 (31)
>20	44 (15)
Percentage of neurosurgical anaesthesia of all anaesthesia services	
<25	49 (17)
25-50	45 (16)
51-75	37 (13)
>75	158 (55)
Number of neurosurgical patients anesthetised per month by me	
<25	61 (21)
25-50	145 (50)
51-100	63 (22)
>100	20 (7)

Variables associated with structured protocol for assessment and management of postoperative pain on univariable analysis were private hospital setup (OR3.20; 95% CI 1.96- 5.23; $P < .001$), higher pain intensity (OR 0.42; 95% CI 0.26-0.68; $P < .001$), doctors performing pain assessment (OR 1.59; 95% CI 0.98-2.56, $P = .059$), use of pain scale (OR 8.25; 95% CI 4.38-15.53; $P < .001$) and use of postoperative opioids (OR 2.29; 95% CI 1.18-4.41; $P = .014$). However, only private setup (OR 2.64; 95% CI 1.52-4.59; $P = .001$), higher pain intensity (OR 0.37; 95% CI 0.21-0.64; $P < .001$) and use of a scale

TABLE 2 Variables associated with use of structured format/protocol for assessment and management of postoperative pain (n = 290)

Factor	Univariable analysis OR (95% CI)	*P* value	Multivariable analysis OR (95% CI)	*P* value
Academic hospital	1.34 (0.67-2.69)	.414		
Private hospital	3.20 (1.96-5.23)	<.001	2.64 (1.52-4.59)	.001
Hospital with >500 beds	0.78 (0.48-1.26)	.312		
Higher pain intensity	0.42 (0.26-0.68)	<.001	0.37 (0.21-0.64)	<.001
Doctor performing assessment	1.59 (0.98-2.56)	.059	1.10 (0.62-1.95)	.750
Use of pain scale	8.25 (4.38-15.53)	<.001	7.94 (3.99-15.81)	<.001
Use of postoperative opioids	2.29 (1.18-4.41)	.014	1.93 (0.90-4.15)	.094

Note: $P < .2$ used for multivariable analysis.

Abbreviations: CI, confidence interval; OR, odds ratio.

TABLE 3 Variables associated with predominant use of opioids for postoperative pain management (n = 289)

Factor	Univariable analysis OR (95% CI)	*P* value	Multivariable analysis OR (95% CI)	*P* value
Academic hospital	1.00 (0.39-2.56)	.995		
Private hospital	2.01 (1.03-3.91)	.041	1.45 (0.66-3.19)	.352
Hospital with >500 beds	0.61 (0.32-1.18)	.140	0.75 (0.36-1.59)	.459
No co-analgesics used	1.06 (0.53-2.12)	.870		
No loco-regional analgesia used[a]				
Use of structured format for pain assessment	2.29 (1.18-4.41)	.014	2.04 (1.02-4.05)	.043

Note: $P < .2$ used for multivariable analysis

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]The factor 'No loco-regional analgesia used' was removed from analysis due to low number of observations for 'no' (n = 15).

for postoperative pain assessment (OR 7.94; 95% CI 3.99-15.81; $P < .001$) were significantly associated with structured pain protocol on multivariable analysis. (Table 2).

Similarly, variables associated with the use of opioids for postoperative pain management on univariable analysis were private hospital setup (OR 2.01; 955 CI 1.03-3.91; $P = .041$), hospital with >500 beds (OR 0.61; 95% CI 0.32-1.18; $P = .140$) and availability of structured protocol for pain assessment (OR 2.29; 95% CI 1.18-4.41; $P = .014$). However, structured pain protocol (OR 2.04; 95% CI 1.02-4.05; $P = .043$) remained the only significant variable for postoperative opioid use on multivariable analysis. (Table 3).

The five most common problems attributable to inadequate postoperative analgesia as per the respondents in this survey were delayed ambulation (n = 96), haemodynamic activation (n = 101), patient dissatisfaction (n = 89), agitation/delirium (n = 80) or a combination of all of these (n = 90) (Figure 1). The three most common reasons for not using postoperative opioids was fear about side effects and inability to monitor and manage them (n = 96), belief that pain is not severe to warrant the use of opioids (n = 67) and surgeons managing postoperative pain and do not prefer to use them (n = 66) (Figure 2). Since the respondents could tick more than one response for questions represented in both the figures, the total number of responses (n) represented in the y-axis is more than 100.

4 | DISCUSSION

In this cross-sectional survey among members of ISNACC, we observed that structured pain protocol after neurosurgery was available and used only in about 41% of the hospitals. Opioid usage for postoperative pain management in neurosurgical patients was very low at 15%. The availability of structured pain protocol was associated with the type of hospital, severity of postoperative pain and use of pain scales while the use of opioids for postneurosurgical pain management was associated with the availability of structured pain protocol.

Many hospitals in high-income nations follow structured postoperative pain protocols and predominantly use opioids for

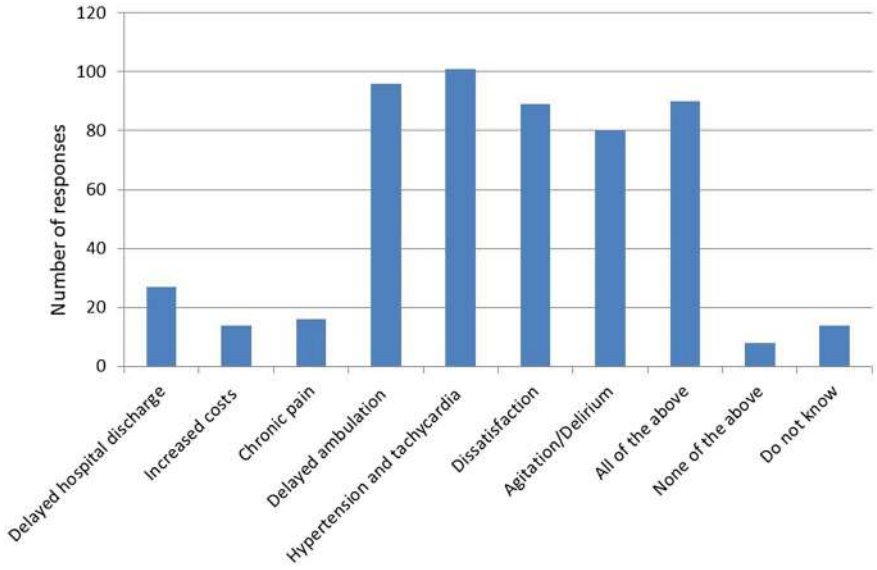

FIGURE 1 Postoperative problems attributable to inadequate analgesia by the responders

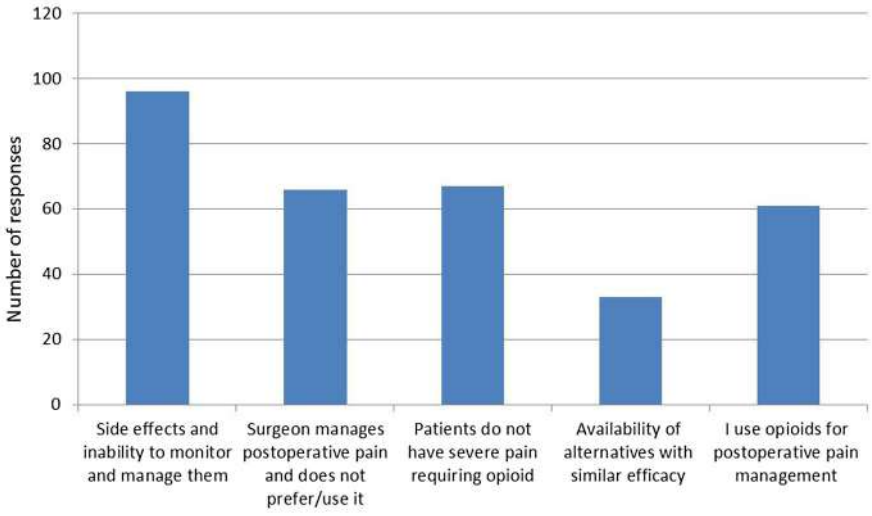

FIGURE 2 Reasons attributed for not using postoperative opioids in neurosurgical patients

postoperative pain management. In contrast, low-to-middle income countries do not have structured documented protocols and predominately use non-opioid analgesia for postoperative pain management after neurosurgery. An earlier study comparing academic with non-academic hospitals demonstrated that academic hospitals have a higher rate (75% vs. 58%) of written postoperative pain protocol than non-teaching hospitals.[11] In our study, we did not observe this finding. However, private hospital setting was more likely than government hospital to have a structured pain protocol in our survey. Unlike government hospitals, most corporate private hospitals in India have accreditation from agencies such as National Accreditation Board for Hospitals and Healthcare Providers or Joint Commission International which mandates having a definite pain assessment/management protocol which can explain our findings. An earlier study has shown positive correlation between hospital beds and acute pain service staff.[12] In this survey, we did not observe any association between hospital bed strength and adoption of structured postoperative pain management.

There are very few surveys on postoperative pain management in neurosurgical settings. In a survey evaluating beliefs and practices of 103 Canadian neurosurgeons regarding postcraniotomy pain management, the most prescribed analgesic was codeine (59%) followed by morphine (38%). Though most (90%) neurosurgeons were satisfied with their choice of analgesic, they reported nausea, constipation and neurologic depression as the most common side effects of these analgesics.[1] In contrast, in our study among anesthesiologists, opioid analgesics were rarely used for postoperative pain management in neurosurgical patients.

A telephonic survey was undertaken in 2009 among nurses of 31 adult neurosurgical units of United Kingdom and neurosurgeons, neuroanesthetists, intensivists and neurosurgery high dependency nurses of King's College Hospital, London to assess practices and perception of postcraniotomy pain management. Seven units (23%) had a standardised analgesic regime/protocol and 20 units (65%) routinely assessed postoperative pain. Analgesia was prescribed on a regular basis in 77% of the units and

when required in others. Codeine or dihydrocodeine was the most common opioid analgesic (22 units, 70%) followed by morphine (9 units, 30%).[3] In contrast, we observed that 41% of hospital setups in our survey had a structured protocol for pain assessment and management and postoperative opioids were used by only 15% of respondents.

A postal questionnaire among senior nurses of 23 neurosurgical directorates within UK in 2005 revealed that intramuscular codeine was the first-line analgesic for postcraniotomy pain.[2] Pain assessment was performed in only 57% of these centres.

Similarly, in a postal survey in 1995 of 183 consultant members of the Neuroanaesthesia Society of Great Britain and Ireland of which 110 neuroanesthetists from 37 neurosurgical centres replied, codeine or dihydrocodeine was the preferred postoperative analgesic by 97% of the respondents despite over half of them reporting that analgesia was inadequate. Only four neuroanesthetists informed about not using postoperative opioids because of fears about respiratory depression and sedation.[4] The most common reason for not using postoperative opioids in our survey was fear about side effects and inability to monitor and manage them in the wards after neurosurgery.

From these surveys, it appears that codeine is the preferred analgesic for postoperative pain management in the UK though its use has decreased from 97% in 1995 to 70% in 2009. These findings are in contrast to what we observed in our survey where majority of the neuroanesthesiologists prefer non-opioid analgesics for pain management after neurosurgery.

In contrast, a postal survey in 2011 among anesthesiologists and neurosurgeons at 44 university hospitals in Korea, non-opioid analgesics were the first-line drugs used for postoperative pain management by neurosurgeons with 52% using NASIDs and 23% using acetaminophen. Only 25% of neurosurgeons used opioids as the first-line analgesic while 50% of anesthesiologists used opioids alone or with NSAIDs as the first-line drug for postcraniotomy pain management.[5] In our study, we observed that majority of neuroanesthesiologists preferred non-opioid analgesics.

It appears that there is a global divide in the way postoperative pain after neurosurgery is managed with preference for opioids in the Western world and Asian countries preferring non-opioid analgesics. The possible reasons for such a difference could be fear of side effects from postoperative opioid use among clinicians in India and Korea or increased pain tolerance among Asian patients due to genetic and ethnic differences. Another important factor for the observed difference in prescription of postoperative analgesics after neurosurgery could be the liberal use of loco-regional analgesia (95% of respondents informed using either scalp block or incision site local anaesthetic infiltration) which reduced opioid administration for postoperative analgesia in our survey.

Differences in pain assessment and management methods can lead to challenges in comparing this important patient outcome for research and practice. Understanding pain assessment and management practices across the country will help clinicians compare their practices with that of their peers and help evaluate performance of perioperative pain management practices at their workplace. Findings of this survey along with data from Indian studies about patient feedback regarding pain relief and satisfaction will help our national neuroanesthesia society to frame practice guidelines for perioperative pain assessment and management.

To our knowledge, this is a first study documenting the practices and preferences regarding pain management after neurosurgery from the developing world. We also assessed factors associated with postoperative opioid use and adoption of structured pain protocol which are uncommon in this part of the world. However, our study has certain limitations. Firstly, we included only the members of ISNACC in this survey and hence our survey would not have captured responses from anesthesiologists who are not ISNACC members and yet provide anaesthesia for neurosurgery in India, though this number is likely to be small. Similarly, we did not administer this survey among neurosurgeons who also manage postoperative pain in many centres. Their approach to postoperative pain is likely to be different from anesthesiologists. Secondly, preferences, practices and perceptions regarding pain management after neurosurgery may vary among caregivers across the world and hence, our findings may not be generalisable to all hospital setups across the world. Thirdly, our questionnaire did not distinguish between pain after cranial and spinal surgeries. Pain management may differ significantly in these two subsets of neurosurgical population. Lack of clarity on some questions might have resulted in skewed responses and this is an important limitation of this study. Lastly, majority (86%) of our respondents belonged to academic hospital setup. This however, reflects the real-world scenario in India of neurosurgical practice being largely restricted to tertiary academic hospitals.

To conclude, less than half of the Indian neuroanesthesiologists who are members of ISNACC use structured format/protocol for pain assessment in neurosurgical patients. Adoption of structured pain protocol was associated with private hospital setup, availability and use of pain scales, and respondents' misperception that postcraniotomy pain is lower in intensity. Similarly, only a small proportion of anesthesiologists (15%) use opioids for pain management after neurosurgery. Having a structured pain protocol was associated with the use of postoperative opioid analgesia. This is in contrast to practices in the western world where use of structured protocols for pain assessment and postoperative opioids for pain management are common in majority of the hospitals.

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DISCLOSURE

The authors have declared no conflicts of interest for this article.

ORCID

Kamath Sriganesh https://orcid.org/0000-0003-2355-0403

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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CHAPTER 3

INCIDENCE, RISK FACTORS AND IMPACT OF ACUTE POSTOPERATIVE PAIN AFTER CRANIAL NEUROSURGERY: A PROSPECTIVE COHORT STUDY

Sriganesh K, Kramer BW, Wadhwa A, Akash V, Bharadwaj S, Umamaheswara Rao G, et al. Incidence, predictors, and impact of acute post-operative pain after cranial neurosurgery: A prospective cohort study. J Neurosci Rural Pract, doi: 10.25259/JNRP_141_2023

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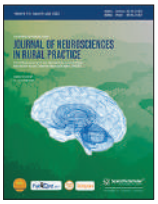

Original Article

Incidence, predictors, and impact of acute post-operative pain after cranial neurosurgery: A prospective cohort study

Kamath Sriganesh[1], Boris W. Kramer[2], Archisha Wadhwa[1], V. S. Akash[3], Suparna Bharadwaj[1], G. S. Umamaheswara Rao[4], Harry W. M. Steinbusch[5], Subhas K. Konar[6], Kadarapura Nanjundaiah Gopalakrishna[1], T. N. Sathyaprabha[7]

[1]Department of Neuroanaesthesia and Neurocritical Care, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India, [2]School of Women's and Infants' Health, University of Western Australia, Australia, [3]Department of Clinical Psychology, All India Institute of Speech and Hearing, Mysuru, [4]Department of Neuroanaesthesia and Neurocritical Care (Retired), National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India, [5]Department of Cellular and Translational Neuroscience, Maastricht University Medical Center, Maastricht, Netherlands, Departments of [6]Neurosurgery and [7]Neurophysiology, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India.

ABSTRACT

Objectives: Pain is common after craniotomy. Its incidence and predictors in developing nations are not adequately studied. We aimed to assess the incidence, predictors, and impact of acute post-operative pain after intracranial neurosurgeries.

Materials and Methods: This prospective observational study was conducted in adult patients undergoing intracranial neurosurgeries. After patient consent, ethics committee approval, and study registration, we assessed the incidence of post-operative pain using numerical rating scale (NRS) score. Predictors and impact of pain on patient outcomes were also evaluated.

Results: A total of 497 patients were recruited during 10-month study period. Significant (4–10 NRS score) post-operative pain at any time-point during the first 3 days after intracranial neurosurgery was reported by 65.5% (307/469) of patients. Incidence of significant pain during the 1st post-operative h, on the 1st, 2nd, and 3rd post-operative days was 20% (78/391), 50% (209/418), 38% (152/401), and 24% (86/360), respectively. Higher pre-operative NRS score and pain during the 1st h post-operatively, predicted the occurrence of pain during the first 3 days after surgery, $P = 0.003$ and $P < 0.001$, respectively. Pain was significantly associated with poor sleep quality on the first 2 post-operative nights ($P < 0.001$). Patient satisfaction score was higher in patients with post-operative pain, $P = 0.002$.

Conclusion: Every two in three patients undergoing elective intracranial neurosurgery report significant pain at some point during the first 3 post-operative days. Pre-operative pain and pain during 1st post-operative h predict the occurrence of significant post-operative pain.

Keywords: Acute post-operative pain, Neurosurgery, Incidence, Predictors, Outcomes

INTRODUCTION

Pain is a common consequence after intracranial neurosurgery. Post-operative pain occurs immediately after surgery and usually lasts till 7 days with maximum incidence and intensity during the first 24–48 h.[1,2]

The incidence of acute post-craniotomy pain is between 30% and 90% and depends on several perioperative factors.[3] Pre-operative elements include pre-existing pain, gender, age, anxiety, depression,[4] cultural background, and health-care environment,[5] while intraoperative factors include type of anesthesia,[6] choice of systemic and locoregional analgesia,[4] use of steroids,[7] and duration and location of surgery.[8] Younger age,[9] female gender,[10] infratentorial surgery,[11] and non-frontal surgery[12] are associated with pain after craniotomy. Post-operative pain can result in significant discomfort and distress to patients and lead to poor in-hospital experience, persistent pain, delayed ambulation and hospital discharge, additional costs, and delirium.[13]

Most previous studies on post-craniotomy pain are from the western population. Many factors which influence post-operative pain are different between developed and developing countries. Sociocultural and ethnic differences affect pain perception differently.[14] Analgesia practices in developing countries differ from developed nations with scalp blocks and non-opioid analgesia being more commonly adopted in the intraoperative period. Non-steroidal anti-

***Corresponding author:** Kamath Sriganesh, Department of Neuroanaesthesia and Neurocritical Care, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India. drsri23@gmail.com

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inflammatory drugs (NSAIDs) and paracetamol (not opioids) are primary analgesics used for post-operative pain treatment in the developing world.[15] These differences might result in different pain incidences, apart from reducing opioid usage.[16] Finally, the burden of pain after intracranial surgery in the Indian subcontinent is not known. This study will fill the current knowledge gap and help in better pain management for our population.

The primary objective of our study was to assess the incidence of acute post-operative pain in adult patients undergoing intracranial neurosurgery. The secondary objectives were to identify potential predictors of pain and assess its impact on in-hospital clinical outcomes.

MATERIALS AND METHODS

This prospective observational study was conducted after obtaining ethics committee approval (NIMHANS/31st IEC (BS and NS DIV.)/2O21 dated 31-August-2021). We registered the study with Clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT05264012) and the Clinical Trial Registry of India (CTRI/2021/09/036525). The current manuscript deals with acute post-craniotomy pain which is part of the project on post-operative pain and neurosurgery.

Consecutive, eligible, and consenting adult patients (≥18 years) undergoing elective intracranial neurosurgeries were recruited. Children, emergency, spine, or surgery under local anesthesia, and patients who cannot/may not respond to our study questions were excluded from the study.

Data regarding age, gender, body mass index, religion, socioeconomic and educational status, domicile, comorbidities, alcohol consumption, pre-operative pain, pre-operative anxiety and depression assessed with hospital anxiety and depression scale, perception about surgery on five-point score, perioperative steroid use, American Society of Anesthesiologists (ASA) grade, surgical site, scalp block, intraoperative opioid dose, use of intraoperative nitrous-oxide or dexmedetomidine, other analgesics (paracetamol, NSAIDs, tramadol), minimum alveolar concentration of volatile anesthetic, durations of surgery and anesthesia were collected from patient's interview, anesthesia information management system and digital patient records.

The primary outcome was the incidence and severity of acute post-operative pain as assessed by numerical rating scale (NRS) score. Pain scores were captured immediately before surgery, in post-anesthesia care unit (PACU) at 15, 30, and 60 min after surgery and for initial 3 days (average and maximum pain during 24-h period). Details regarding post-operative analgesics were obtained. For the purpose of this study, we categorized NRS score 0–3 as no/mild (insignificant) pain and NRS score 4–10 as moderate-to-severe (significant) pain. The impact of significant pain on in-hospital clinical outcomes was evaluated. Following outcome measures were assessed: Duration of post-operative hospital stay, quality of sleep on the first 2 post-operative nights on 1–10 scale (10 being extremely good sleep), patient satisfaction on 1–10 scale (10 being highly satisfied), and day of ambulation after surgery.

With the average incidence of post-craniotomy pain reported as 60% in the literature,[3] and considering possible 5% margin of error, sample size of 368 was considered necessary to achieve 95% confidence level.[17] We expected maximum dropout of 15% for our primary outcome from non-extubation or abnormal consciousness after surgery impending pain assessment. Hence, we adjusted our sample size to 433 patients using formula n*1/(1–0.15).

Data collected was stored in a Microsoft Excel worksheet and analyses were performed using the Statistical Package for the Social Sciences v.28 statistical package. We evaluated the normality of data with Shapiro–Wilk test. Results are expressed as mean ± standard deviation, median and interquartile range or number and percentage (%). Differences between the two groups (significant vs. insignificant pain) were tested using *t*-test or Mann–Whitney test for continuous data and ordinal variables and Chi-square test for categorical variables. Logistic regression was performed to identify predictors of significant pain. $P < 0.05$ was considered as statistically significant.

RESULTS

A total of 497 patients participated in this study from September 2021 to June 2022. Data regarding primary pain outcome were available for 469 patients. No pain scores were available for 25 patients due to the inability to assess pain at any time-point (non-extubation, abnormal consciousness) during the first 3 post-operative days and surgery was abandoned in three patients [Figure 1].

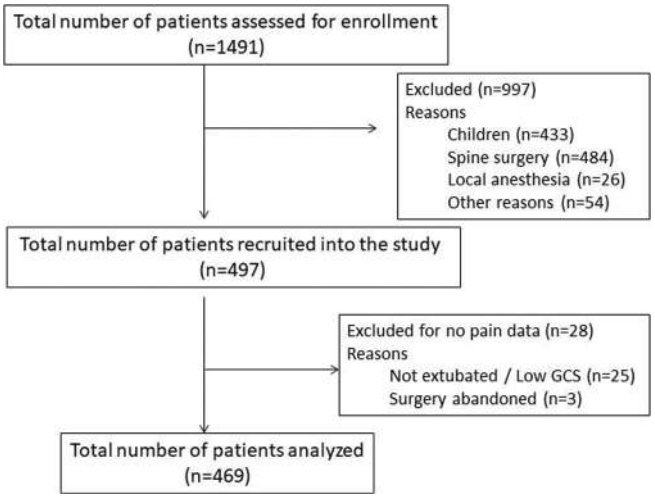

Figure 1: Diagram demonstrating flow of patients in our study.

Significant post-operative pain at any assessment time-point during first 72-h period after cranial neurosurgery was reported by 65.5% (307/469) patients. Incidence of significant pain during the first 1 h after surgery, on the 1st, 2nd, and 3rd post-operative days was 20% (78/391), 50% (209/418), 38% (152/401), and 24% (86/360), respectively. Patients available for pain assessment varied across 3 days due to poor neurological status, non-extubation, or early hospital discharge.

The median NRS scores were 0 (0–3) versus 5 (4.75–6) between insignificant and significant pain groups in the first 1 h. The median NRS scores were 1 (1–2) versus 3 (2–5) and 0 (0–3) versus 5 (5–7) for average and maximum NRS scores, respectively, on the 1st post-operative day between the two groups. The average and maximum median NRS scores were 0 (0–3) versus 4 (3–5) and 0 (0–3) versus 5 (5–6) for day 2, and 0 (0–3) versus 4 (3–5) and 3 (0–3) versus 5 (5–5) for day 3 after surgery, respectively. Most patients received fixed-dose regimen of diclofenac (n = 357), followed by paracetamol (n = 63), and both diclofenac and paracetamol (n = 9) in post-operative period. Figure 2 demonstrates median NRS scores across various time-points in patients with and without significant pain after brain surgery.

The risk factors with potential for association with acute significant post-operative pain after intracranial surgery on univariate analysis are shown in [Table 1]. No difference was noted between the groups for site and approach of surgery (frontal and parietal vs. temporal and occipital craniotomy vs. trans-nasal trans-sphenoidal surgery) or type of post-operative non-opioid analgesics (diclofenac, paracetamol or both). No patient received opioids during the first 3 post-operative days. On univariate analysis; pre-operative pain, anxiety, depression, non-usage of steroids, and pain during the first 1-h after surgery were associated with the occurrence of significant pain in initial 3 post-operative days ($P < 0.1$). These factors were analyzed using multivariate regression to identify predictors of acute significant pain. Only pre-operative pain and pain during initial 1 h after surgery remained predictors of significant post-operative pain [Table 2]. Pre-operative pain (headache) was reported by 19% of patients in the insignificant pain group and 34.4% of patients in the significant pain group. The effect of significant pain on clinical outcomes is informed in [Table 3]. There was no difference in the duration of hospital stay or day to ambulation, but patients with significant pain had lower scores for post-operative sleep. Satisfaction was, however, better in patients with significant pain.

DISCUSSION

Despite pain being a common problem after craniotomy, only few studies evaluated post-operative pain in detail. Most previous studies had small sample size, were retrospective in nature, published decades ago, were from developed world, and evaluated few risk factors. One study involving 37 patients

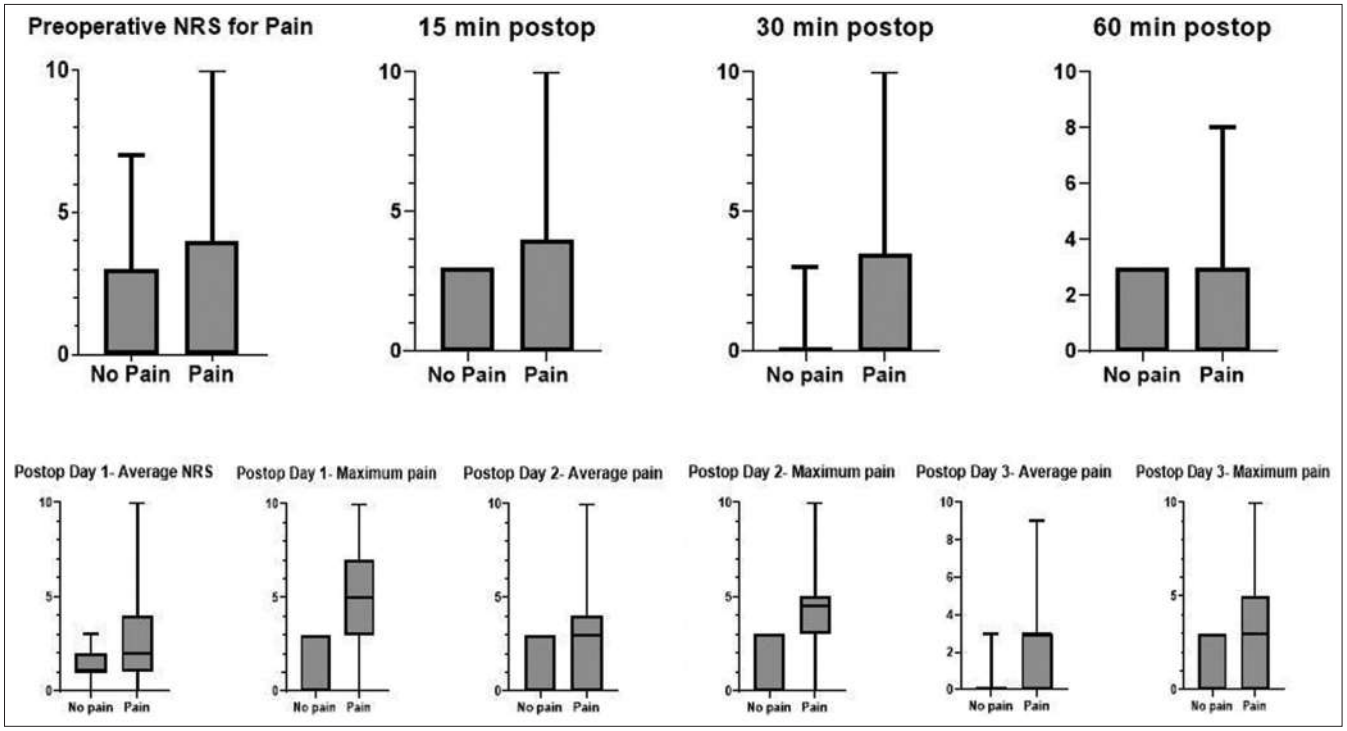

Figure 2: Box plot showing comparison of numerical rating scale scores (median and interquartile range) for pain at different assessment time-points.

Table 1: Comparison of predictors for significant acute post-operative pain after intracranial neurosurgery on univariate analysis.

Variables	Insignificant pain	Significant pain	*P*-value
Age (years)	42 (31–54)	42 (32–50)	0.770
Female gender	76 (47%)	151 (49%)	0.698
BMI (kg/m^2)	24.28 (22.04–26.47)	24.14 (22.04–26.53)	0.606
Hindu religion	148 (91%)	267 (87%)	0.148
Rural domicile	138 (85%)	264 (89%)	0.245
Illiterate status	32 (20%)	77 (25%)	0.250
Unemployed status	101 (63%)	188 (61%)	0.765
Below poverty line status	92 (57%)	196 (64%)	0.301
Chronic alcoholism history	8 (5%)	21 (7%)	0.546
ASA grade	2 (2–2)	2 (2–2)	0.160
Pre-operative NRS pain score	0 (0–3)	0 (0–4)	<0.001
Pre-operative anxiety score	0 (0–7)	3 (0–9)	<0.001
Pre-operative depression score	0 (0–6)	0 (0–7)	0.066
Positive perception score about surgery	5 (5–5)	5 (4–5)	0.278
Infratentorial craniotomy	32 (20%)	67 (22%)	0.636
Pre-operative scalp block	93 (58%)	194 (63%)	0.272
Intraoperative morphine dose (mg/kg/h)	0.05 (0.03–0.10)	0.06 (0.03–0.10)	0.318
Intraoperative nitrous-oxide use	24 (15%)	37 (12%)	0.391
Intraoperative dexmedetomidine use	33 (21%)	58 (19%)	0.712
Perioperative steroid use	51 (32%)	134 (44%)	0.013
Surgery duration (h)	3.45 (2.4–5)	3.48 (2.5–4.4)	0.614
Intraoperative MAC of anesthetic	0.9 (0.8–1.0)	0.9 (0.8–1.0)	0.290
Maximum NRS score during 1st h after surgery	0 (0–3)	0 (0–4)	<0.001

BMI: Body Mass Index, ASA: American Society of Anesthesiologists, NRS: Numerical rating scale, MAC: Minimum alveolar concentration. Values expressed as mean±standard deviation, median and interquartile range or number (percentage)

Table 2: Predictors of significant acute post-operative pain after brain surgery on multivariate analysis.

Variables	B	S.E.	Wald	df	Sig.	Exp (B)	95%CI	
							Lower	Upper
Maximum NRS pain score in 1st post-operative hour	0.223	0.052	18.28	1	<0.001	1.250	1.129	1.385
Pre-operative NRS pain score	0.153	0.051	9.05	1	0.003	1.165	1.055	1.287
Pre-operative anxiety score	0.027	0.026	1.11	1	0.292	1.028	0.977	1.081
Pre-operative depression score	−0.025	0.034	0.56	1	0.455	0.975	0.913	1.042
Perioperative steroid use	0.293	0.233	1.58	1	0.209	1.340	0.849	2.117

NRS: Numerical rating scale, S.E.: Standard error, df: Degrees of freedom, Sig.: Significant, CI: Confidence interval

Table 3: Comparison of clinically important outcomes between significant and insignificant pain groups after intracranial neurosurgery.

Variables	Overall insignificant pain	Overall significant pain	*P*-value
Duration of post-operative hospital stay (days)	6 (3.5–10)	5 (3–8)	0.193
Sleep quality on night-1 after surgery	6 (4–7)	5 (3–7)	<0.001
Sleep quality on night-2 after surgery	7 (5–8)	6 (5–7)	<0.001
Patient satisfaction score	5.5 (5–6)	6 (5–8)	0.002
	Day-wise no significant pain (%)	**Day-wise significant pain (%)**	***P*-value**
Day-1 ambulation	112 (54)	105 (51)	0.492
Day-2 ambulation	166 (67)	112 (74)	0.180
Day-3 ambulation	215 (81)	67 (78)	0.643

Values expressed as median and interquartile range or number (percentage)

noted 60% incidence of post-operative pain with two-thirds reporting it as moderate-to-severe and maximum pain during the first 48 h after brain surgery.[9] A 64% incidence of pain was observed among 58 patients[18] and 192 patients,[19] with

both studies involving acoustic neuroma surgery. Another study in 256 patients noted 55% incidence of moderate-to-severe pain during the first 24 h after craniotomy.[6] Similarly, 69% and 48% incidences of significant pain (NRS ≥4) on the 1st and 2nd day, respectively, were observed after intracranial surgery in 187 patients.[2] Our incidence of 65% in larger sample is similar to that reported in earlier studies suggesting that despite recent advances, post-craniotomy pain remains a challenge in perioperative patient care. Previous studies reported the use of post-operative opioids for analgesia along with non-opioid drugs.[6,7,20] Pain incidence in our study was not different despite non-usage of post-operative opioids. This suggests that non-opioid analgesia fare similarly in providing pain relief in the presence of locoregional analgesia.

Pre-operative pain predisposes to post-craniotomy pain.[8,19] This finding was noted in our study too. Hence, it is important to assess and manage pre-operative pain effectively to reduce the development of post-operative pain.

Females[9] and younger patients[6,8,9] had higher incidence of pain after intracranial surgery. The median age of our study population was 42 years, and age did not predict post-operative pain. An earlier study too did not observe age contributing to post-operative pain.[21] We did not observe association between gender and pain which is similar to earlier studies.[6,8] One study noted ASA Grade III patients reporting more pain than ASA Grade I.[8] This was not seen in our study.

Pain is a personal experience; pain behavior and response are influenced by previous experiences, beliefs, expectations, sociocultural and psychological factors, and caregiver attitude.[5,14,22,23] Anxiety and depression can affect post-operative pain.[3,24] However, previous reports are conflicting in craniotomy patients.[9,25] We observed that pre-operative anxiety but not depression was associated with post-operative pain on univariate analysis. Unemployment and less education were associated with post-operative pain in orthopedic patients.[26] We did not observe association of religion, socioeconomic status, education, and domicile with post-operative pain.

Infratentorial[2,21] and non-frontal surgeries[12] are associated with post-operative pain. However, we did not observe effect of surgical site (supratentorial vs. infratentorial, and between supratentorial sites - frontal and parietal [less muscle retraction] vs. temporal and occipital [more muscle retraction] vs. trans-nasal trans-sphenoidal [minimally invasive]) on post-operative pain. This finding matches with an earlier study.[6]

Scalp block or incision site infiltration reduces analgesic requirement and post-operative pain.[11] Scalp block reduces the nociceptive response to skull pin insertion better than pin-site infiltration.[27] Another study demonstrated decreased intraoperative opioid consumption but similar post-operative pain with scalp block when compared to local infiltration.[28] We did not see the difference in post-operative pain between patients receiving and not receiving scalp block. This could be due to all patients receiving incision site local anesthetic infiltration in our study.

The use of non-opioid analgesics during surgery results in similar post-operative pain scores as compared to opioids.[29] Dexmedetomidine use reduces opioid requirements during craniotomy.[30] However, intraoperative opioid dose and dexmedetomidine use were similar in our patients with and without significant post-operative pain. Nitrous-oxide use did not influence post-operative pain in our study. We observed lower incidence of post-operative pain on univariate analysis with perioperative steroid use. This is in line with earlier reports[6,7] and reflects the mechanism of prostaglandin synthesis inhibition, anti-inflammatory effect, increased endorphins, and mood alteration contributing to beneficial effects on pain perception. We did not observe relationship between surgery duration and post-operative pain. This finding was similar to previous study.[6] Earlier studies were inconsistent about risk factors for pain after intracranial surgery. One study in 47 patients undergoing brain tumor surgery could not identify any predictors for post-operative pain.[31] Despite larger sample, assessing more factors, and including different intracranial procedures, we found only pre-operative pain and pain during the first post-operative hour as predictors of significant pain.

Post-operative pain results in longer hospital stays and delayed ambulation after hip fracture surgery.[32] However, we did not observe association between post-operative pain, hospital stay, and ambulation. Unlike in patients undergoing hip surgery where operative site pain directly affects ambulation, post-operative pain may not necessarily preclude ambulation after craniotomy. In the absence of delayed ambulation, hospital discharge time was also similar.

There are no previous studies evaluating sleep and pain after intracranial surgeries. Post-operative pain resulted in poor sleep among patients undergoing orthopedic[33] and arthroplasty surgeries.[34] Sleep quality score was significantly lower on the first two post-operative nights in patients with significant pain vis-à-vis insignificant pain in our study. This emphasizes the need for good pain relief irrespective of type of surgery to improve post-operative sleep.

A previous survey of post-operative pain and patient satisfaction across all types of surgeries from India documented high satisfaction rates despite >65% of patients experiencing pain.[35] Similar findings were reported earlier where despite significant pain, patients did not appear dissatisfied.[23] However, one study noted poor patient satisfaction with higher pain.[2] The median satisfaction scores

in our study were comparable clinically (6 vs. 5.5) in patients with and without significant pain but were statistically different. Patient satisfaction assessment in this study was not specific to pain but included overall perioperative care. This suggests that satisfaction is more likely aligned with patient expectations and how they are met, than actual pain experienced after surgery.

The strength of this study is its large, prospective observational nature assessing several perioperative factors and evaluation of impact of pain on clinical outcomes. However, this study has certain limitations. Average and maximal pain was assessed for the first 3 post-operative days. More frequent assessments and for longer periods might provide more insight into pattern of pain distribution and experience. Our hospital does not have acute pain services and post-operative opioids are not routinely administered. Despite this, we observed similar incidence of post-operative pain to that reported in previous studies where post-operative opioids were used. Comparison of combined loco-regional and non-opioid analgesia versus opioids for post-operative pain requires further investigation.

CONCLUSION

Two-thirds of patients undergoing elective intracranial neurosurgery report significant pain at some point during the first 3 post-operative days. For effective post-operative pain management, it is important to address pre-operative pain and ensure pain relief continues in PACU. Post-operative pain affects sleep quality but not ambulation or hospital stay after craniotomy. Despite significant pain, patient satisfaction may be higher if expectations are met. Anesthesiologists, neurosurgeons, and nurses involved in perioperative care should be aware of the magnitude of post-operative pain and its influence on post-operative course and put more efforts in addressing modifiable risk factors to reduce acute post-operative pain.

Declaration of patient consent

Institutional Review Board (IRB) permission was obtained for the study.

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Conflicts of interest

There are no conflicts of interest.

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CHAPTER 4

ANALGESIA NOCICEPTION INDEX AND SYSTEMIC HAEMODYNAMICS DURING ANAESTHETIC INDUCTION AND TRACHEAL INTUBATION: A SECONDARY ANALYSIS OF A RANDOMISED CONTROLLED TRIAL

Sriganesh K, Theerth KA, Reddy M, Chakrabarti D, Rao GS

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Original Article

Analgesia nociception index and systemic haemodynamics during anaesthetic induction and tracheal intubation: A secondary analysis of a randomised controlled trial

Address for correspondence:
Dr. Kamath Sriganesh, Department of Neuroanaesthesia, Faculty Block, 3rd Floor, National Institute of Mental Health and Neurosciences, Hosur Road, Bengaluru - 560 029, Karnataka, India.
E-mail: drsri23@gmail.com

Kamath Sriganesh, Kaushic A Theerth[1], Madhusudan Reddy, Dhritiman Chakrabarti, Ganne Sesha Umamaheswara Rao

Department of Neuroanaesthesia and Neurocritical Care, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, [1]Department of Neuroanaesthesia and Neurocritical Care, Rajagiri Hospital, Ernakulam, Kerala, India

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ABSTRACT

Background and Aims: Direct laryngoscopy and tracheal intubation is a noxious stimulation that induces significant stress response. Currently, this nociceptive response is assessed mainly by haemodynamic changes. Recently, analgesia nociception index (ANI) is introduced into anaesthesia practice and provides objective information about parasympathetic (low nociceptive stress) and sympathetic (high nociceptive stress) balance, which reflects the degree of intraoperative nociception/analgesia. This study evaluated the changes in ANI and haemodynamics during anaesthetic induction and intubation, and their correlation during tracheal intubation. **Methods:** Sixty adult patients scheduled for elective brain tumour surgery under general anaesthesia were studied for changes in ANI, heart rate (HR) and mean blood pressure (MBP) during anaesthetic induction and intubation. This was a secondary analysis of a previously published trial. Linear mixed effects model was used to evaluate changes in ANI, HR and MBP and to test correlation between ANI and haemodynamics. **Results:** Anaesthetic induction reduced ANI (but not below the critical threshold of nociception of 50) and MBP, and increased the HR ($P < 0.001$). Direct laryngoscopy and tracheal intubation resulted in increase in HR and MBP with decrease in ANI below the threshold of 50 ($P < 0.001$). A linear negative correlation was observed between ANI and HR; $r = -0.405$, $P < 0.001$, and ANI and MBP; $r = -0.415$, $P = 0.001$. **Conclusion:** Significant changes are observed in ANI during anaesthetic induction and intubation. There is a negative linear correlation between ANI and systemic haemodynamics during intubation.

Key words: Anaesthetic induction, analgesia nociception index, craniotomy, intubation, noxious stimulation

INTRODUCTION

Direct laryngoscopy and tracheal intubation (DLTI) is an essential component of general anaesthesia for neurosurgery. Despite the therapeutic dose of opioid analgesic and adequate depth of anaesthesia, significant stress response is common during noxious stimulation from DLTI.[1] This response can be detrimental in at-risk patients such as those with cardiovascular co-morbidities and intracranial pathologies.[2] Clinically, changes in the haemodynamic parameters such as tachycardia and hypertension are considered as indicators of nociceptive response to DLTI. Other surrogate tools such as catecholamine levels,[3] heart

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rate variability (HRV),[4] surgical pleth index (SPI),[5] difference in the state and response entropy,[6] have been explored to assess nociception during DLTI. Analgesia nociception index (ANI) has recently been explored to assess nociception during perioperative period. The ANI is an electrophysiological monitoring tool which provides a 0 to 100 score based on the spectral analysis of HRV; where 0 reflects minimal parasympathetic tone with maximal stress response and nociception, and 100 represents maximal parasympathetic tone with minimal stress response and nociception.[7] There are no previous studies which have examined specifically and in detail, the changes in ANI during DLTI. Previous studies lacked information about time points studied (both before and after intubation),[8,9] or examined ANI only at one time point after intubation[10] necessitating the need for this detailed study.

The primary objective of this study was to evaluate changes in ANI during anaesthetic induction and DLTI in patients undergoing craniotomy for supra-tentorial brain tumours. The secondary objectives were to evaluate changes in haemodynamics; heart rate (HR) and mean blood pressure (MBP), and correlate changes in the ANI with changes in the haemodynamics during DLTI.

METHODS

This is a secondary analysis of a previously published randomised controlled trial evaluating ANI-guided fentanyl consumption in patients undergoing craniotomy with scalp block (n = 30) and incision site infiltration (n = 30).[11] In brief, the current study is a pooled data analysis of all patients (n = 60) undergoing anaesthetic induction followed by DLTI for craniotomy at a tertiary neurosciences centre in India. The institutional ethics committee approved the study and the trial was registered with the Clinical Trial Registry of India - CTRI/2018/01/011299.

All consecutive consenting patients aged between 18 and 65 years of either sex were recruited if they were scheduled for elective craniotomy for brain tumours over an 18 months period (May 2015 to Oct 2016). Presence of diabetes mellitus, systemic hypertension, significant arrhythmias, chronic pain, allergy to local anaesthetics, coagulopathy, scalp infection, previous craniotomy, pacemaker, pregnancy, and medications affecting the autonomic system were exclusions for this study.

The ANI provides measurement of analgesia/nociception balance, with higher values reflecting increased parasympathetic activity (analgesia) and lower values corresponding to sympathetic activation (nociception).[12] The ANI monitor (MetroDoloris Medical Systems, Lille, France) displays two parameters, the ANIi which is ANI instantaneous (single value) and the ANIm, which is the mean ANI obtained by a 2 minute averaging of ANIi. The ANI > 50 predicts adequate analgesia.[13]

After the patients were wheeled into the operating room, standard monitors (electrocardiogram, pulse oximeter and non-invasive blood pressure) were established. The ANI electrodes were applied at V1 and V5 electrocardiographic positions as per the recommendations of the manufacturers. All patients received fentanyl 2 μg/kg intravenous (IV) and thiopentone 5 mg/kg IV for anaesthetic induction followed by vecuronium 0.15 mg/kg IV for facilitating intubation. This anaesthetic induction protocol is followed in our institution for neurosurgeries in this population and we did not deviate from this practice for the purpose of this study. The DLTI was performed 3 minutes later by one anaesthesiologist with more than 4 years of experience using an appropriate size (3 or 4) Macintosh laryngoscope blade at 1 minimum alveolar concentration (MAC) of sevoflurane with 50% nitrous-oxide in oxygen. Sevoflurane was started soon after intravenous anaesthetic induction and maintained at 1 MAC (between 1.8 to 2.2 end expired sevoflurane concentration) till the completion of intubation. Following completion of data collection regarding DLTI, and 8 minutes before skull pin fixation, local anaesthetic scalp block or pin site infiltration was performed.

We collected data regarding HR, MBP and ANI just before the thiopentone administration and at 1, 2, and 3 minutes after thiopentone to assess the effect of anaesthetic induction on these parameters. Similarly, data regarding HR, MBP and ANI were collected at following time points: just before insertion of laryngoscope (pre-laryngoscopy), during laryngoscopy (intubation 0 minute), and at 1, 2, 3, 4 and 5 minutes after intubation.

No formal sample size was estimated for this explorative secondary analysis. Data was collated offline on a Microsoft Excel spreadsheet for analysis and SPSS version 17 was used for statistical analysis. Interval scale variables are represented as

mean ± standard deviation and categorical variables as percentages and frequencies. Preliminary data visualization as line trends for all variables for individual patients demonstrated variation in slopes of change over time and hence, linear mixed effects models incorporating random intercepts and slopes to account for variation in dependent variable due to between patient variability were chosen for analysis. The estimation and hypothesis testing for fixed effect of time on the variables was done in two sets – 4 time points for anaesthetic induction using thiopentone and 7 time points for DLTI. Maximum likelihood method was used, assuming scaled identity covariance matrix structure, with random slopes and intercepts incorporated. The same procedure was used for observing correlations between the variables, with use of HR and MBP as predictor variables for prediction of ANIi. A $P < 0.05$ was taken as level of statistical significance.

RESULTS

The complete data was available for 57/60 patients and was analysed. The data in 3 patients was lost due to technical issue with ANI sensors and use of vasopressor for managing hypotension. There was no difficulty with mask ventilation in the study population. All patients were successfully intubated in first attempt by the same operator with either 3 or 4 size Macintosh laryngoscope blade. The mean age (years) of the study population was 38.83 ± 14.79, weight (kg) was 59.63 ± 9.13 and 29 (50.9%) patients belonged to the male gender.

There were significant changes ($P < 0.001$) in the measured parameters- HR, MBP, ANIi and ANIm after anaesthetic induction as compared to baseline [Table 1]. After anaesthetic induction, the HR increased immediately with trend returning towards baseline value at 3 minutes. The MBP decreased with anaesthetic induction and remained significantly lower than baseline value at 3 minutes after induction. Both ANIi and ANIm decreased with anaesthetic induction but the values remained above the threshold of nociception (50).

Significant changes ($P < 0.001$) were observed for all four parameters- HR, MBP, ANIi and ANIm after DLTI as compared to baseline values [Table 2]. The HR increased immediately and significantly with DLTI, was maximal at 2 minutes and gradually decreased without reaching the baseline value. The MBP increased starting with DLTI, reached the maximum at 1 minute and returned to baseline value at 5 minutes after DLTI. The ANIm decreased significantly with DLTI but remained above the critical threshold of 50 throughout the measured time-points. However, ANIi decreased immediately and significantly, remaining below 50 till 2 minutes and increased gradually to reach close to the baseline value by 5 minutes after DLTI.

There was a linear negative correlation between ANIi and HR over all time-points for all patients [correlation estimate = −0.405, standard error = 0.052, $P < 0.001$ [Figure 1]. Similarly, there was a linear negative correlation between ANIi and MBP over all time-points

Table 1: Changes in the study variables in 57 patients during anaesthetic induction (mean±standard deviation)

Time point	HR (bpm)	MBP (mmHg)	ANI Mean	ANI Instantaneous
Pre-induction	77.23±13.15	91.91±20.87	66.25±11.46	65.75±12.84
Thiopentone 1 min	82.91±13.78	81.89±11.45	62.33±18.07	51.82±21.82
Thiopentone 2 min	80.88±10.56	81.88±13.98	57.14±20.09	49.32±16.04
Thiopentone 3 min	79.32±10.73	76.84±14.46	50.21±10.60	50.12±15.06
P	<0.001	<0.001	<0.001	<0.001

P<0.05 is statistically significant

Table 2: Changes in the study variables in 57 patients during laryngoscopy and tracheal intubation (mean±standard deviation)

Time point	HR (bpm)	MBP (mmHg)	ANI Mean	ANI Instantaneous
Pre-laryngoscopy	74.02±9.99	74.51±12.41	57.77±13.71	59.98±16.15
Intubation 0 min	86.23±14.68	85.64±18.14	55.37±13.32	47.68±24.16
Intubation 1 min	89.11±17.53	94.67±25.45	53.16±14.66	39.60±11.05
Intubation 2 min	89.81±16.03	90.12±22.07	49.95±13.10	43.74±13.22
Intubation 3 min	87.16±16.05	82.09±14.96	49.65±13.61	50.35±19.74
Intubation 4 min	82.56±16.56	79.18±13.03	52.96±17.56	53.00±17.89
Intubation 5 min	81.53±14.83	76.82±14.32	53.89±19.00	55.11±17.95
P	<0.001	<0.001	<0.001	<0.001

P<0.05 is statistically significant

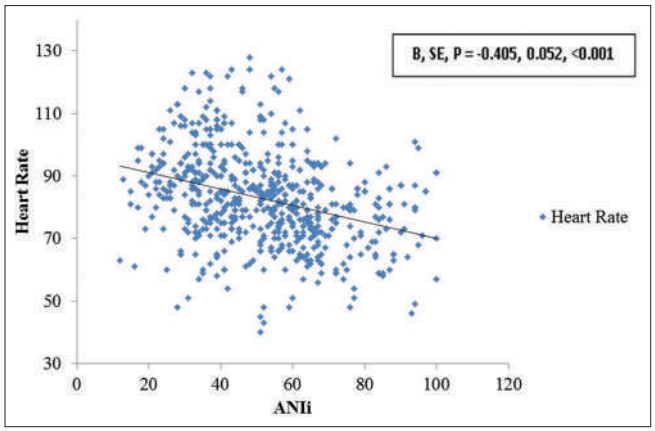

Figure 1: Scatter plot between heart rate and ANI instantaneous over all time-points for all patients. B – Coefficient estimate, SE – standard error, *P* – *P* value. *P* < 0.05 is statistically significant

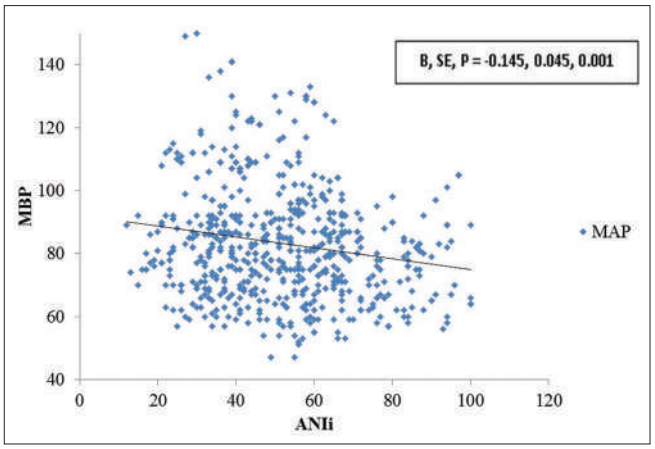

Figure 2: Scatter plot between mean blood pressure and ANI instantaneous over all time-points of all patients. MBP – mean blood pressure, B – coefficient estimate, SE – standard error, *P* – *P* value. *P* < 0.05 is statistically significant

for all patients [correlation estimate = −0.415, standard error = 0.045, *P* = 0.001 [Figure 2].

DISCUSSION

We observed increase in HR, and reduction in MBP and ANI values with anaesthetic induction. Our observations are in agreement with the findings of previous studies. An earlier study demonstrated reduction in total HRV with greater depression of HRV_{high} component as compared to HRV_{low} after anaesthetic induction with thiopentone 4 mg/kg with 60% nitrous-oxide in oxygen indicating a greater depressant effect on parasympathetic reflexes (vagolytic effect) as compared to sympathetic system with this technique.[14] Similarly, a significant reduction in high frequency (HF) vis-à-vis low frequency (LF) power was observed after propofol or thiopentone induction in 47 patients.[15] Another study involving 100 patients observed that fentanyl administered during anaesthetic induction decreased total and LF power indicating greater suppression of sympathetic activity while thiopentone increased LF power demonstrating vagolytic effect (increased sympathetic activity).[16] In our study, thiopentone was administered immediately after fentanyl and the overall effect predominantly reflected the vagolytic effect with decrease in ANI.

We observed significant decrease in ANIm and ANIi with increase in HR and MBP during DLTI despite clinically acceptable depth of anaesthesia and analgesia. Similar findings were noted by Ledowski *et al*. during airway manipulation in 30 patients with ANIi decreasing from 52 to 33 ($P < 0.001$) at 30 s after intubation.[10] No further time point other than at 30 s was studied to understand the magnitude and pattern of change. Further, data regarding ANI was missing in 43% (13/30) of patients studied resulting in small sample of 17 patients. In a recent study involving 21 neurosurgical patients, the mean ANI decreased from 68 at induction to 52 after intubation.[8] Here again, the changes specific to DLTI were not studied and the time point of measurement of ANI is not clear for both the pre-intubation value, and the post-intubation value. Another study published in non-English language observed ANI of 44 and 39 after intubation in propofol and sevoflurane group respectively, both below the threshold of 50.[9] In this study too, the pre- and post-intubation time point of ANI measurement was not reported. Our study specifically addressed the limitations of these previous studies with regards to the time pattern of change in the ANI and haemodynamics starting from just before DLTI, through the intubation process and then every minute for five minutes after intubation which provided comprehensive impact (magnitude and direction of change) of DLTI on ANI. Boselli *et al*. also observed a significant decrease in ANI from 72 to 46 ($P < 0.01$) during suspension laryngoscopy as compared to baseline during anaesthesia with propofol-remifentanil anaesthesia.[17] In this study no intubation was performed and no neuromuscular blocking drug was used making it different from our study population. However, in our study too, the ANI decreased below the threshold of 50 despite 1 MAC of sevoflurane and adequate analgesia (ANI >50) before intubation.

We observed a significant negative linear correlation between ANI and HR, and ANI and MBP during DLTI in

this study. A similar negative correlation is documented between ANI and systemic haemodynamics during periods of noxious stimulation in the intraoperative period,[8] and between ANI and postoperative pain as assessed by numerical rating scale score after general anaesthesia.[9,18,19]

The strength of this study is that this study specifically and in detail evaluated the effect of DLTI on ANI and haemodynamic parameters during anaesthesia, unlike previous studies. ANI monitoring provides objective assessment of the balance between pain and analgesia during periods of noxious stimulus such as laryngoscopy and intubation unlike the changes in the systemic haemodynamics, which can manifest from other causes. We also noted that the conventional dose of potent opioid analgesic (2 μg/kg fentanyl IV) is inadequate in ablating the nociceptive response to DLTI as assessed by ANI. The major limitation of this study is the inability to assess the potential impact of transitional state from spontaneous respiration to apnoea to controlled ventilation on ANI during anaesthetic induction and DLTI. Secondly, we excluded patients with likely affection of autonomic nervous system from drugs or diseases such as diabetes mellitus and hypertension. The ANI changes and haemodynamic response might vary differently in these populations for the similar noxious stimulus of DLTI. Lastly, we did not explore the impact of certain confounders such as Cormack Lehane grade, experience of the operator performing the intubation and duration of laryngoscopy. These are important parameters that determine laryngoscopy response which this secondary analysis did not capture. Poor Cormack Lehane grade, less experience of intubation and prolonged duration of laryngoscopy are likely to result in more nociception. These aspects need to be evaluated in future studies.

Use of ANI as a monitoring modality helps assess the magnitude of pain and adequacy of analgesia objectively unlike changes in the heart rate and blood pressure during noxious stimulation of laryngoscopy and intubation. Further studies are needed to evaluate optimal dose of potent opioids in ablating nociceptive response to DLTI and to assess impact of pre-determined airway characteristics on ANI during intubation.

CONCLUSION

Significant increase in heart rate, and decrease in blood pressure and ANI were observed after anaesthetic induction as compared to baseline. Heart rate and blood pressure increased significantly and ANIi and ANIm decreased significantly during tracheal intubation with 2 μg/kg of fentanyl dose. There was a negative linear correlation between ANI and systemic haemodynamics during intubation.

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Conflicts of interest

There are no conflicts of interest.

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Announcement

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30 Sept 2019	ISA Goldcon Quiz	Chairperson, Scientific Committee ISACON 2019
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CHAPTER 5

EFFECT OF OPIOID VERSUS NON-OPIOID ANALGESIA ON SURGICAL PLETH INDEX AND BIOMARKERS OF SURGICAL STRESS DURING NEUROSURGERY FOR BRAIN TUMORS: PRELIMINARY FINDINGS

Sriganesh K, Syeda S, Shanthanna H, Venkataramaiah S, Palaniswamy SR

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Effect of Opioid Versus Non-Opioid Analgesia on Surgical Pleth Index and Biomarkers of Surgical Stress During Neurosurgery for Brain Tumors: Preliminary Findings

Kamath Sriganesh, Seham Syeda, Harsha Shanthanna[1], Sudhir Venkataramaiah, Sangeetha R Palaniswamy

Department of Neuroanesthesia and Neurocritical Care, National Institute of Mental Health and Neurosciences, Bengaluru, India, [1]Department of Anaesthesia, McMaster, University, Hamilton, ON, Canada

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

Abstract:

Background: Stress response to surgery is mediated by the sympathetic nervous system and manifests as changes in hemodynamic and neuroendocrine parameters. Recently, the surgical pleth index (SPI) is employed for objective and continuous monitoring of nociceptive response during surgery. Opioids are the mainstay of managing stress response to nociception during the perioperative period. However, due to the well-known adverse effects of opioids, $\alpha 2$ agonists are increasingly used to ablate stress response and reduce opioid usage.

Objectives: This study compared SPI and biomarkers of surgical stress between opioid (fentanyl) and non-opioid (dexmedetomidine) analgesia during craniotomy.

Methods: Patients aged 18 to 60 years undergoing elective craniotomies for brain tumor resection under general anesthesia were randomized to receive fentanyl 1 μg/kg/h or dexmedetomidine 0.5 μ/kg/h infusion as the primary intraoperative analgesic. Our objective was to compare SPI and biomarkers of surgical stress—serum cortisol, blood glucose, arterial pH, and leucocyte count between the two groups.

Results: Data of all 24 patients recruited into the study were analyzed. There was no difference in the demographic parameters between the groups. The SPI remained similar with both the drugs over various time points during the study period. There was no difference between the groups in the biomarkers of surgical stress—cortisol, blood glucose, and pH while leucocyte count was higher in the fentanyl group.

Conclusions: The stress response to surgery during craniotomy for brain tumors is similar with opioid (fentanyl) and non-opioid (dexmedetomidine) analgesia as assessed by SPI and blood markers such as cortisol, glucose, and pH.

Key Words:

Biomarkers, neurosurgery, non-opioid analgesia, stress response, surgical pleth index

Key Message:

The nociceptive response as assessed by the surgical pleth index and stress response to surgery as assessed by blood biomarkers is similar with opioid (fentanyl) and non-opioid (dexmedetomidine) analgesia during craniotomy for brain tumor resection.

Noxious stimuli associated with surgery elicit sympathetically mediated stress response that can adversely affect perioperative outcomes.[1] Measuring surgical stress and nociception during the intraoperative period, though important, is not routinely adopted due to a lack of readily available intraoperative stress/nociception monitor. The current surrogates for assessing surgery-induced nociceptive response under anesthesia such as lacrimation, sweating, movement, and increase in heart rate (HR) and blood pressure (BP) are non-specific and unreliable. Recently, an objective parameter, the surgical stress index (SSI) has been used to assess stress response during surgery.[2] The SSI assesses intraoperative stress using photoplethysmographic waveform

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amplitude and heart beat-to-beat interval,[3] and is marketed as surgical pleth index (SPI) in commercially available monitors. The SPI allows quantification of stress response to surgery and hence, effectively any changes to stress response by medications or other interventions.

Apart from hemodynamic activation resulting in tachycardia and hypertension, surgical stress response also manifests as a wide range of endocrinological, immunological, and hematological changes.[4] Among the several neuroendocrine indicators for surgical stress that have been reported, such as pituitary and adrenal hormones, the most commonly studied biomarkers include blood glucose and serum cortisol. Other surrogate markers of surgical stress that can be easily assessed include blood pH and leucocyte count (LC).[5,6]

Opioids are the primary analgesics used to minimize stress response to nociception elicited during the perioperative period. However, due to well-known adverse effects associated with opioids,[7] dexmedetomidine, an alpha-2 agonist, is increasingly used alone,[8-10] or as an opioid-sparing adjuvant during neurosurgeries.[11] Dexmedetomidine, by reducing sympathoadrenal and cardiovascular responses to noxious surgical stimuli, minimizes stress response mediated by the sympathetic nervous system.[4] Additionally, dexmedetomidine reduces opioid consumption and opioid-associated undesirable effects. Also, it is relatively cheaper and easily available, making it accessible in low- and middle-income countries. Despite its potential, dexmedetomidine has not yet replaced opioids for intraoperative analgesia during neurosurgeries. We recently conducted a trial comparing fentanyl and dexmedetomidine in patients undergoing craniotomy for brain tumors and found them comparable for postoperative analgesia.[8] No study has however evaluated the effect of analgesics on stress response and nociception using SPI in the neurosurgical population.[8,12]

The objectives of this study were to compare intraoperative nociception using SPI and surgical stress response using biomarkers between opioid (fentanyl) and non-opioid (dexmedetomidine) analgesia during elective neurosurgery for a brain tumor.

Methods

This study is a secondary analysis of our published study[8] comparing fentanyl and dexmedetomidine as a primary intraoperative analgesic for perioperative pain relief and opioid consumption during elective craniotomies. The study received a research grant from the Academy of Regional Anaesthesia of India (2017), and the trial was registered with the Clinical Trial Registry of India (CTRI/2017/12/010833). Following ethics committee approval [NIMHANS/IEC (BS & NS DIV) 8th meeting 2017 dated 26-08-2017] and informed consent, patients aged between 18 and 60 years undergoing elective supratentorial brain tumor decompression surgery were screened in March and April 2018. Consented patients were randomized in a 1:1 allocation ratio using a computer-generated random number table by an anesthesiologist not directly involved in the trial, to receive either fentanyl or dexmedetomidine. All patients received standard anesthetic induction with thiopentone 5 mg/kg, fentanyl 1 μg/kg, lignocaine 1.5 mg/kg, and vecuronium 0.1 mg/kg followed by maintenance with oxygen/air/isoflurane titrated to an anesthetic depth of 40-60 on entropy monitor. Bilateral scalp block was performed in all patients after anesthetic induction with 30 mL of 1% lignocaine with 1:200000 epinephrine and 0.25% bupivacaine. The study interventions were administered as fentanyl 1 μg/kg/h or dexmedetomidine 0.5 μg/kg/h, starting from anesthetic induction to skin closure. Hemodynamic activation (>25% increase in HR or mean BP (MBP) from baseline) during surgery despite adequate anesthetic depth was managed with a fentanyl bolus of 50 μg. Apart from standard parameters such as HR, BP, oxygen saturation, end-tidal carbon dioxide, and anesthetic agent levels, SPI was also monitored from a multiparameter patient monitor. Our outcome measures were changes in SPI during surgery and markers of stress response—serum cortisol, random blood glucose (RBG), arterial pH, and LC.

Surgical pleth index

The SPI (GE Healthcare, Helsinki, Finland) is a score for assessing intraoperative nociception and ranges from 0 to 100, with 100 corresponding to high stress level and 0 corresponding to absent stress. It is computed from normalized heartbeat interval (HBI_{norm}) and plethysmographic pulse-wave amplitude ($PPWA_{norm}$) and is derived as follows: SSI = 100–(0.7*$PPWA_{norm}$ + 0.3*HBI_{norm}).[3] The SPI appears to be a better measure of nociception/antinociception balance than entropy and HR,[2] and therefore is used to monitor nociceptive stress response to surgery and titrate intraoperative analgesic administration.

Biomarkers of stress response

The biomarkers of surgical stress that we evaluated were serum cortisol, RBG, pH, and LC. All samples were collected from an indwelling arterial cannula. The random serum cortisol was measured using electro chemiluminescence immune-assay method from Cobas e-411 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). The RBG was measured using point of care device, NOCODING One-plus Blood Glucose Meter (ISENS Biosensors India Pvt. Ltd, Gurgaon, India). The pH was obtained from the Eschweiler Combiline blood gas analyzer (Eschweiler GmbH & Co, Kiel, Germany). The LC was estimated in our Clinical Laboratory using an automated hematology analyzer (Beckman Coulter, Miami, USA).

Data collection

Baseline demographic characteristics were obtained at the time of consent for all patients. Data regarding SPI were collected every 15 minutes from the beginning to the end of anesthesia. Biomarkers of stress response were collected just before and immediately after the surgery.

Statistical analysis

Since this is a preliminary study, no formal sample size was calculated. The collected data were collated offline on the Microsoft Excel worksheet. Continuous variables are represented as means ± standard deviations (SDs) or medians and interquartile ranges (IQRs), depending on normality of distribution of our data as assessed by Shapiro–Wilk test, and categorical variables as frequencies and percentages. We performed repeated-measures analysis of

variance (RMANOVA) for within-group SPI data over various timepoints and mixed model ANOVA for between-group and interaction analysis for SPI. Independent samples *t* test or Mann–Whitney U tests were used as appropriate to compare between the two groups for the post-pre difference in cortisol, RBG, pH, and LC. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 17 (SPSS Inc., Chicago, IL) and $P < 0.05$ was considered statistically significant.

Results

The data of all patients recruited into the study were analyzed. Figure 1 depicts patient flow into the study. Twenty patients were operated for frontal, temporal or temporoparietal glioma, three for meningioma and one for third ventricle cystic lesion. The mean (SD) age in years in fentanyl and dexmedetomidine group was 42.3 (14.8) and 42.9 (11.3), respectively and mean (SD) weight in kilograms was 62.9 (9.8) and 63.4 (13.8), respectively. The proportion of males in the fentanyl and dexmedetomidine group was six (50%) and eight (66.7%), respectively. Six patients in fentanyl and five patients in dexmedetomidine group received additional fentanyl bolus in the intraoperative period.

Surgical pleth index

The SPI remained below the threshold of 50 at all timepoints during surgery in both the groups [Figure 2]. There was no significant change in SPI with time in both fentanyl ($F = 0.995$, $\eta^2 = 0.083$, $P = 0.461$) and dexmedetomidine ($F = 0.847$, $\eta^2 = 0.078$, $P = 0.618$) group. Similarly, there was no difference in SPI between fentanyl and dexmedetomidine groups ($F = 0.508$, $\eta^2 = 0.024$, $P = 0.484$ and for group*time interaction $F = 1.170$, $\eta^2 = 0.672$, $P = 0.427$) suggesting that surgical stress response as evaluated by SPI remained similar with both the drugs over various timepoints of study period.

Biomarkers of Surgical Stress

The changes in biomarkers of surgical stress are shown in Table 1. Serum cortisol level did not change significantly in both groups with analgesic drug infusion. Cortisol level (μg/dL) reported as median and IQR before and after fentanyl infusion was 0.51 (0.39 to 0.67) and 0.51 (0.35 to 4.05), respectively. Similarly, cortisol level before and after dexmedetomidine infusion was 4.28 (0.37 to 14.42) and 2.43 (0.28 to 16.43), respectively. The post-pre difference (median and IQR) in cortisol levels in fentanyl and dexmedetomidine group were -0.09 (-0.19 to 0.37) and -0.03 (-0.21 to 3.19), with $P = 1.000$ and 0.937, respectively for within-group change. There was no significant difference between fentanyl and dexmedetomidine groups for post-pre cortisol differences; $P = 0.630$.

The RBG level increased significantly in both groups during surgery. The RBG level (mg %) reported as mean ± SD before and after fentanyl infusion was 71.67 ± 22.28 and 102.75 ± 24.27, respectively. Similarly, RBG levels before and after dexmedetomidine infusion were 80.33 ± 20.08 and 116.92 ± 25.42, respectively. The post-pre differences (mean ± SD) in RBG levels in the fentanyl and dexmedetomidine group were 31.08 ± 26.91 and 36.58 ± 22.59 with $P = 0.002$ and <0.001, respectively for within-group change. There was no significant difference between fentanyl and dexmedetomidine groups for post-pre RBG difference (MD: 5.5; 95% CI of difference -26.532, 15.532; $P = 0.593$).

The arterial pH decreased non-significantly in both groups during surgery. The arterial pH before and after fentanyl infusion (median and IQR) was 7.41 (7.39 to 7.49) and 7.38 (7.34 to 7.45), respectively. Similarly, pH before and after dexmedetomidine infusion was 7.46 (7.42 to 7.52) and 7.41 (7.40 to 7.47), respectively. The post-pre difference (median and IQR) in pH in fentanyl and dexmedetomidine group was 0.035 (-0.02 to 0.08) and 0.06 (-0.01 to 0.11) with $P = 0.158$ and 0.213, respectively for within-group change. There was no significant difference between fentanyl and dexmedetomidine groups for the post-pre pH difference; $P = 0.551$).

The LC increased in both the groups, with a significant increase in the fentanyl group during surgery. The LC ($10^3/\mu L$) reported as mean ± SD before and after fentanyl infusion was 9.00 ± 3.53 and 16.40 ± 7.39, respectively. Similarly, LC ($10^3/\mu L$) before and after dexmedetomidine infusion was10.67 ± 4.20 and 12.97 ± 5.44, respectively. The post-pre differences (mean ± SD) in LC ($10^3/\mu L$) in fentanyl and dexmedetomidine groups were 7.4 ± 1.46 and 2.3 ± 1.40 with $P < 0.001$ and 0.134, respectively for within-group change. There was significant difference between fentanyl and dexmedetomidine groups for post-pre LC difference (MD 5.09; 95% CI of difference 0.814, 9.366; $P = 0.022$).

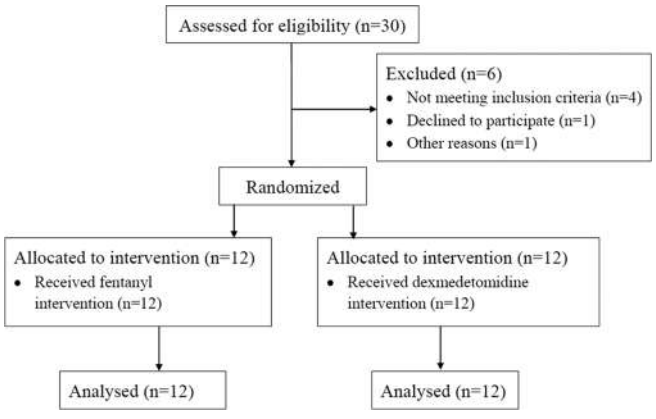

Figure 1: Flow diagram depicting patient flow into the study

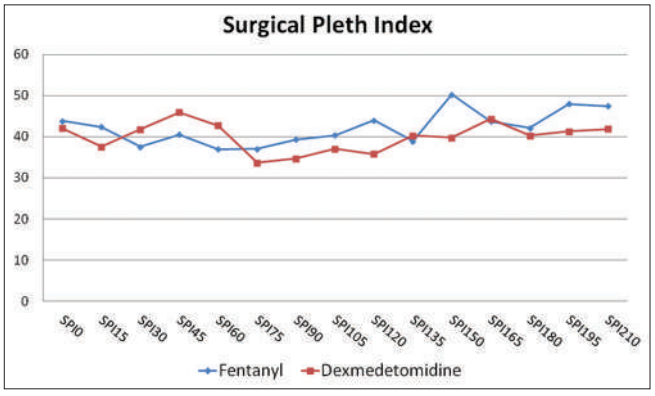

Figure 2: Surgical pleth index in the fentanyl and dexmedetomidine group over the infusion timeperiod during surgery

Table 1: Post-Pre change (after discontinuation and before the beginning of infusion) in the biomarkers of surgical stress with fentanyl and dexmedetomidine analgesia during neurosurgery

Measured parameters	Fentanyl (*n*=12)	Dexmedetomidine (*n*=12)	*P*
Serum cortisol (μg/dL)	-0.09 (-0.19 to 0.37)	-0.03 (-0.21 to 3.19)	0.630
Random blood glucose (mg %)	31.08±26.91	36.58±22.59	0.593
Arterial pH	-0.04 (-0.02-0.08)	-0.06 (-0.08 to 0.11)	0.551
Leucocyte count (10^3/μL)	7.40±1.46	2.30±1.40	0.022

Values are expressed as mean±standard deviation or as median (interquartile range) as applicable; *P*<0.05 is significant

Discussion

In this study comparing opioid (fentanyl) and non-opioid (dexmedetomidine) drugs for intraoperative analgesia during elective craniotomies, we found no differences in intraoperative stress response to surgery as assessed by SPI and biochemical stress markers of serum cortisol, RBG, and arterial pH. The postoperative LC showed a statistically significant increase in fentanyl group as compared to the dexmedetomidine group, perhaps more as a chance than a true finding.

The SPI has been well-studied as a measure of intraoperative nociception and as a parameter to titrate intraoperative analgesics. In a study comparing SPI-guided versus standard analgesia for laparoscopic cholecystectomy, the authors noted lower SPI values after pneumoperitoneum insufflation but other parameters such as remifentanil consumption, postoperative pain, and recovery from anesthesia were similar.[13] Similarly, Jain *et al.* compared SPI-guided fentanyl analgesia technique with conventional analgesia technique during laparoscopic cholecystectomy. Patients in the SPI group received fentanyl 0.5 μg/kg to maintain SPI between 20 and 50 while patients in the conventional group received fentanyl 0.5 μg/kg when either HR or MBP increased by 20% from baseline. Although intraoperative fentanyl consumption was significantly higher, postoperative visual analog scale score and adjuvant fentanyl requirement were significantly lesser in the SPI group as compared to the conventional group. Drug-related adverse events were similar in both groups.[14] In another study comparing SPI-guided analgesia with conventional analgesia technique in children undergoing adenotonsillectomy, the authors observed reduced fentanyl requirement but similar sevoflurane consumption in the SPI group. However, postoperative emergence agitation and pain were significantly more in the SPI group.[15] In our study, both groups had SPI measurements however, analgesic titration was made based on changes in hemodynamics. We did not find any difference in SPI at any time-point between fentanyl and dexmedetomidine suggesting a similar degree of nociception and analgesia in both the groups. A combination of entropy and SPI results in fewer episodes of hypotension, reduced vasopressor requirement, and fewer doses of fentanyl boluses in critically ill polytrauma patients[16] and should be used when feasible.

Surgical stress results in sympathetic activation and increased adrenal production of cortisol. A recent meta-analysis involving 71 studies with 2953 patients demonstrated that surgical stress response is more pronounced in older patients, women, and in those undergoing open surgery and general anesthesia.[17] However, the anesthetic technique can independently influence stress markers. Total intravenous anesthesia (TIVA) with propofol-remifentanil reduced stress markers of cortisol and glucose as compared to inhalational (isoflurane-remifentanil) technique in patients undergoing laparoscopic surgery.[18]

There are limited data on stress response during neurosurgery with regards to the anesthetic technique. In a study evaluating stress response during craniotomy with two anesthetic techniques, authors observed significantly higher glucose levels with isoflurane-remifentanil when compared to propofol-remifentanil in contrast to similar cortisol levels at various time-points studied.[19] Similar findings were noted in another recent study evaluating stress response to neurosurgery in normotensive and hypertensive patients. Stress markers such as C-reactive protein, blood glucose, and leucocyte levels were reduced with TIVA (propofol-fentanyl infusion) when compared to balanced anesthesia (isoflurane-intermittent fentanyl) technique.[20] We did not observe the difference between fentanyl and dexmedetomidine in the stress markers we studied (cortisol, RBG, and pH) except LC, which was increased in the fentanyl group.

Very few studies have evaluated the effect of intraoperative analgesia on stress response to surgery. Similar changes in hemodynamics and stress hormones—adrenocorticotrophic hormone (ACTH), cortisol, growth hormone, and prolactin were noted in a study comparing two doses of remifentanil infusion, 0.15 and 0.3 μg/kg/min, in 50 patients undergoing laparoscopic cholecystectomy.[21] Similarly, in a study comparing remifentanil with alfentanil TIVA, no difference in plasma concentrations of cortisol, insulin, and glucose was observed in 24 patients undergoing abdominal hysterectomy.[22] We did not observe a difference in stress markers to craniotomy in our study comparing opioid (fentanyl) with non-opioid (dexmedetomidine) analgesia. This finding could be a result of similar surgical stress during craniotomy in both the groups as demonstrated by comparable SPI values. However, a study comparing three analgesic techniques- scalp block, pin-site infiltration and rescue opioid administration for skull-pin insertion, noted significantly reduced levels of stress hormones (ACTH and cortisol) after pin insertion with scalp block.[23]

Our study has important strengths. This is perhaps the first study comparing stress response during neurosurgery using SPI and biomarkers in patients receiving opioid (fentanyl) with non-opioid (dexmedetomidine) analgesia. These outcomes demonstrate that non-opioid analgesia with dexmedetomidine is not inferior to fentanyl, not only in subjective outcomes as observed in our feasibility study,[8] but also in objective measurements of the surgical stress response. This study, however, has several limitations. The small sample size is a major limitation of this trial. Second, we did not compare all

biomarkers of stress response to surgery. Third, given the small number, we did not perform sub-group analysis to evaluate the effect of operative site of craniotomy on the biomarkers of surgical stress. Lastly, the scalp block in both groups may have influenced stress response independent of our study drugs. However, this study encourages further work to generate more robust evidence on this clinically important topic.

Conclusions

There were no differences in surgical stress response as measured by SPI and serum biomarkers of stress between opioid (fentanyl) and non-opioid (dexmedetomidine) analgesia during brain tumor surgery. Future studies comparing opioid with non-opioid analgesia for stress response to surgery as the primary outcome are required to validate our preliminary findings.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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CHAPTER 6

COMPARISON OF INTRAOPERATIVE FENTANYL WITH DEXMEDETOMIDINE FOR PERIOPERATIVE ANALGESIA AND OPIOID CONSUMPTION DURING CRANIOTOMIES: A RANDOMISED CONTROLLED PILOT STUDY WITH NON-INFERIORITY DESIGN

Sriganesh K, Syeda S, Shanthanna H, Venkataramaiah S, Palaniswamy SR

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Comparison of intraoperative fentanyl with dexmedetomidine for perioperative analgesia and opioid consumption during craniotomies: A randomised controlled pilot study with non-inferiority design

Kamath Sriganesh[1] | Seham Syeda[1] | Harsha Shanthanna[2] | Sudhir Venkataramaiah[1] | Sangeetha R. Palaniswamy[1]

[1]Department of Neuroanaesthesia and Neurocritical Care, National Institute of Mental Health and Neurosciences, Bengaluru, India

[2]Department of Anaesthesia, McMaster University, Hamilton, ON, Canada

Correspondence
Kamath Sriganesh, Department of Neuroanaesthesia and Neurocritical Care, National Institute of Mental Health and Neurosciences, Bengaluru, India.
Email: drsri23@gmail.com

Funding information
Academy of Regional Anaesthesia of India

Abstract

Background: Moderate to severe pain is common despite the use of potent opioids during craniotomies. Non-opioid agents such as dexmedetomidine reduce undesirable opioid effects and are successfully used as primary analgesic during bariatric surgeries. This study assessed the feasibility of conducting a large randomised controlled trial comparing fentanyl with dexmedetomidine for perioperative analgesia during craniotomy.

Methods: This was a prospective single-centre randomised controlled feasibility trial. Twenty-four consenting adult patients undergoing supratentorial craniotomy at NIMHANS, Bangalore, India, were recruited after ethical approval in March and April 2018. They received either fentanyl 1 $\mu g\ kg^{-1}\ h^{-1}$ (n = 12) or dexmedetomidine 0.5 $\mu g\ kg^{-1}\ h^{-1}$ (n = 12) as primary intraoperative analgesic drug. Patient, anaesthesiologist, outcome assessor and data analyst were blinded to the study intervention. Our feasibility outcomes (primary) were recruitment and adherence rates. We also explored the potential efficacy of intervention and adverse events.

Results: We recruited 24 out of 30 eligible patients and had 100% protocol adherence, thereby demonstrating the feasibility of a larger randomised controlled trial. All 24 patients completed the study. The demographic and clinical parameters were similar between the groups. Compared between fentanyl and dexmedetomidine, there was no difference in the intraoperative fentanyl (top-up) consumption (μg), expressed as median and interquartile range: 25 (0-50) and 0 (0-50); $P = 0.844$; and no difference in postoperative pain at 15 and 60 minutes. Adverse events were few and similar with fentanyl and dexmedetomidine.

Conclusions: A large-scale randomised controlled trial of perioperative dexmedetomidine versus fentanyl is feasible. Dexmedetomidine has the potential to be non-inferior to fentanyl for perioperative analgesia during craniotomies.

1 | INTRODUCTION

Moderate to severe pain occurs in up to 80% of patients after neurosurgery despite liberal use of perioperative opioids.[1,2] While opioids reduce nociceptive response and provide analgesia during surgery, they are often associated with undesirable effects such as postoperative nausea and vomiting (PONV), decreased gastro-intestinal motility, delayed recovery, pruritis, sedation and respiratory depression.[2,3] Therefore, measures to avoid opioid analgesia are increasingly incorporated in the analgesic regimen to overcome these problems. Previous studies have noted comparable analgesia with non-opioid analgesics such as ketamine, dexmedetomidine and lignocaine alone or in combination when compared with opioids in bariatric and laparoscopic surgeries.[4-6] For neurosurgical procedures, addition of dexmedetomidine to an opioid-based technique resulted in less adverse effects and reduction in anaesthetic and perioperative opioid consumption.[7-9] Currently, there is no evidence to support the use of dexmedetomidine as a primary analgesic during craniotomies. An earlier study observed similar haemodynamics and adverse events but longer time to postoperative opioid requirement with dexmedetomidine when compared to remifentanil during neurosurgery. However, intraoperative opioid consumption and postoperative pain scores were not evaluated.[10] Therefore, there is a need for a well-designed randomised controlled trial (RCT) to establish whether dexmedetomidine is an effective substitute for opioids for intraoperative pain management during neurosurgery. Before embarking on a large RCT, it is important to explore the study feasibility with a pilot RCT. We hypothesised that dexmedetomidine as a sole analgesic is feasible and is non-inferior to fentanyl as an intraoperative analgesic with fewer adverse effects when used along with scalp block during supratentorial neurosurgery.

The primary objective was to evaluate the feasibility of a larger study. Secondary objectives were (a) assessment of non-inferiority in terms of intraoperative opioid requirements, (b) comparison of postoperative analgesia, (c) incidence of drug-related adverse outcomes and (d) quality of recovery.

What's known

- Moderate to severe pain is common after craniotomy. Opioids are the mainstay for management of perioperative pain. Opioids are associated with certain adverse effects which are undesirable in this population.

What's new

- This paper demonstrates that a large scale trial comparing fentanyl with dexmedetomidine for perioperative analgesia is feasible. Dexmedetomidine has the potential to be non-inferior to fentanyl for perioperative analgesia after craniotomy.

2 | MATERIALS AND METHODS

2.1 | Ethical approval and informed consent

The study was approved by the NIMHANS ethics committee and recruited patients consented for participation in this study.

2.2 | Setting

The study was conducted at the National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, India. NIMHANS is a large tertiary care, neurosciences institute operating more than 5000 neurosurgical procedures every year.

2.3 | Trial Registration

The study was registered with the Clinical Trial Registry of India (CTRI/2017/12/010833).

2.4 | Funding

This study received research grant from Academy of Regional Anaesthesia of India.

2.5 | Trial design

This prospective study was a randomised, single-centre, parallel-group, pilot RCT.

2.6 | Study participants

All consecutive consenting adult patients of either sex, aged between 18 and 60 years, scheduled for elective craniotomy for supratentorial tumour decompression in supine or lateral position were included in this study. The recruitment was conducted in March and April 2018. Patients were excluded if they were unwilling or if they had a current or recent history of ischaemic heart disease, cardiac failure (New York Heart Association grade ≥3), heart block or arrhythmia, uncontrolled hypertension (>140/90 mmHg) and diabetes mellitus (glycosylated haemoglobin >6.5%) despite treatment, emergency surgery, co-existing chronic pain conditions receiving long-term pain medications on a daily basis, history of motion sickness, previous craniotomy, and opioid dependence as per the Diagnostic and Statistical Manual of mental disorders IV criteria.

2.7 | Recruitment

The attending anaesthesiologist screened potential participants considered for elective craniotomies during the preoperative

assessment and informed our research assistant for possible enrollment and consenting.

2.8 | Control of potential bias

Randomisation was performed using a computer-generated random number table with 1:1 allocation ratio by an anaesthesiologist not directly involved in the trial or patient care. The group allocation list was discreetly shared with the anaesthesia technician (not involved in the intraoperative management), who prepared the study drug syringes as per the sequence number and assigned patients to the trial groups. Both the study drugs were prepared in an identical 50 cc syringe as colourless solutions and provided to the operating room anaesthesiologist for administration to ensure blinding. Patient was subsequently followed up by a researcher who was unaware of the group allocation. Thus effectively, the patient, anaesthesiologist, outcome assessor and the data analyst were blinded to the group allocation.

2.9 | Data collection

Baseline data including diagnosis, current medications, imaging findings, neurological status and demographic data (age, weight and gender) were collected during preanaesthetic evaluation. Data collected during the perioperative period included type of surgery, intraoperative bolus fentanyl consumption, numerical rating scale (NRS) score for pain at 15 and 60 minutes and 24 and 48 hours after surgery, adverse events such as perioperative hypo or hypertension, brady or tachycardia, PONV, respiratory depression, pruritis, shivering and recovery characteristics after anaesthesia including emergence agitation or sedation, delayed recovery and coughing.

2.10 | Study interventions

Patients received either fentanyl 1 μg kg^{-1} h^{-1} or dexmedetomidine 0.5 μg kg^{-1} h^{-1} during the entire surgery beginning with anaesthetic induction till skin closure as the primary intraoperative analgesic drug as per the randomisation, administered using an infusion pump.

2.11 | Conduct of anaesthesia

Anaesthetic induction was performed with thiopentone 5 mg/kg and lignocaine 1.5 mg/kg and intubation was facilitated with vecuronium 0.1 mg/kg. In all patients fentanyl 1 μg/kg was administered to attenuate haemodynamic response to laryngoscopy. Anaesthesia was maintained with oxygen: air: isoflurane titrated to an anaesthetic depth of 40-60 on spectral entropy monitor. Attending anaesthesiologist performed bilateral scalp blocks with a combination of 1% lignocaine with 1:200000 adrenaline and 0.25% bupivacaine (total volume of 30 mL) to block the sensory nerves supplying the scalp area (supraorbital, supratrochlear, zygomatico-temporal, auriculo-temporal, greater auricular and greater and lesser occipital nerves) before skull-pin application. Any haemodynamic activation (either blood pressure or heart rate of >25% from baseline) during surgery despite adequate depth of anaesthesia was managed by administering a 50 μg fentanyl bolus and the total dose administered was documented. At dural closure, patients in both the groups received 1 g paracetamol and 4 mg ondensetron, phenytoin 100 mg and dexamethasone 8 mg. At the end of surgery, the incision site was infiltrated with 0.125% bupivacaine for postoperative analgesia in all patients. Patients were evaluated for quality of recovery by assessing time to extubation, time for response to verbal commands, presence or absence of emergence agitation and coughing during extubation and haemodynamics.

2.12 | Post anaesthesia care unit (PACU) management

All patients were monitored in the PACU for at least 60 minutes and their postoperative outcome measures were assessed by a blinded anaesthesiologist. Postoperative NRS score (0-10) was assessed at 15 and 60 minutes after arrival to the PACU. Our analgesic protocol was to administer diclofenac 1 mg/kg intravenously if NRS was >3 and tramadol 2mg/kg if NRS persisted >3 even after 15 minutes. The emergence quality was assessed by Richmond Agitation Sedation Scale (RASS) score (−5 to +4). Patients were monitored for drug-related adverse events till PACU discharge such as brady/tachycardia and hypo/hypertension (25% change from baseline), PONV, sedation, shivering, pruritis, and respiratory depression. Postoperative shivering was graded as described by Wrench et al[11]: 0 = no shivering, 1 = piloerection but no visible muscle activity, 2 = one muscle group twitches, 3 = more than one muscle group twitching and 4 = whole body movement. Treatment plan included tramadol 1mg/kg and active warming using forced air warming device set at 40°C if score was >2. PONV was assessed using 0-3 score[12]: 0 = no PONV, 1 = nausea only, 2 = vomiting, 3 = >1 episode of vomiting and ondensetron 4 mg administered for scores >1. Pruritis was assessed using NRS (0-10) with 0 = no itching and 10 = severe itching with NRS >3 being treated with 22.75 mg of pheniramine maleate. Respiratory depression was considered when respiratory rate was <8 per minute and if present, end tidal carbon dioxide monitoring was performed and patient electively ventilated if end-tidal carbon-dioxide level remained >45 mmHg.

2.13 | Outcome measures

The primary outcome measures assessed to establish feasibility were, (a) patient recruitment: ≥80% recruitment [feasibility of recruiting ≥80% of study sample in 4 months] and (b) protocol adherence: ≥80% adherence [protocol violation was described as needing to stop study drug for any reason including safety and efficacy resulting in attrition]. The secondary outcome measures were exploratory and assessed the effectiveness of the study intervention in terms of non-inferiority to continuous fentanyl infusion: (a) total bolus fentanyl administration during surgery and (b) differences in the postoperative NRS score at 15 and 60 minutes of PACU

admission. Our tertiary outcome measures included (a) pain scores at 24 and 48 hours after surgery and (b) safety outcomes: incidence of perioperative hypotension/hypertension and bradycardia/tachycardia, incidence of PONV, shivering, respiratory depression, and pruritis; and recovery characteristics as described above.

2.14 | Sample size

As this was a pilot study, sample size was not based on hypothesis testing. Based on feasibility considerations, we planned to include 12 patients/group suggested as appropriate in literature for pilot studies.[13,14]

2.15 | Statistical analysis

We used an intent-to-treat analysis along with a per protocol analysis. The normality of the data was tested with Shapiro-Wilk test and if normally distributed, data were described as mean and standard deviation and if not normally distributed, reported as median and interquartile range (IQR). Feasibility outcomes were assessed with descriptive statistics (frequencies, percentages). Appropriate parametric or non-parametric tests were applied. The categorical variables are expressed as numbers and percentages and analysed using a Chi-squared test or Fischer's test. For exploratory efficacy analysis, the non-inferiority margin for the between-group difference for cumulative additional fentanyl dose was set at margin of 100 μg. Statistical significance for clinical outcomes was tested with a one-sided test with an alpha value of 0.025. All statistical analysis was performed using statistical package for social sciences version 16.

3 | RESULTS

Thirty consecutive patients were approached for recruitment during the study period. The rate of recruited patients among eligible- 24/30 (80%) satisfied our feasibility parameters. The reasons for exclusion of six patients were: patient did not consent (n = 1), multiple brain lesions (n = 1), significant cardiovascular co-morbidity (n = 1), scheduled for surgery in prone position (n = 1) and older than 60 years (n = 2). (Figure 1) Our exclusion of a patient with multiple brain lesions was not planned but was clinically appropriate. Because these patients could be operated in different positions, we considered this as an exclusion criterion for our main trial. All 24 patients, as 12 in each group, completed the study without any loss to follow-up. The demographic and clinical characteristics of included patients are shown in Table 1. All 24/24 (100%) patients completed the study without any protocol violation. We demonstrated feasibility

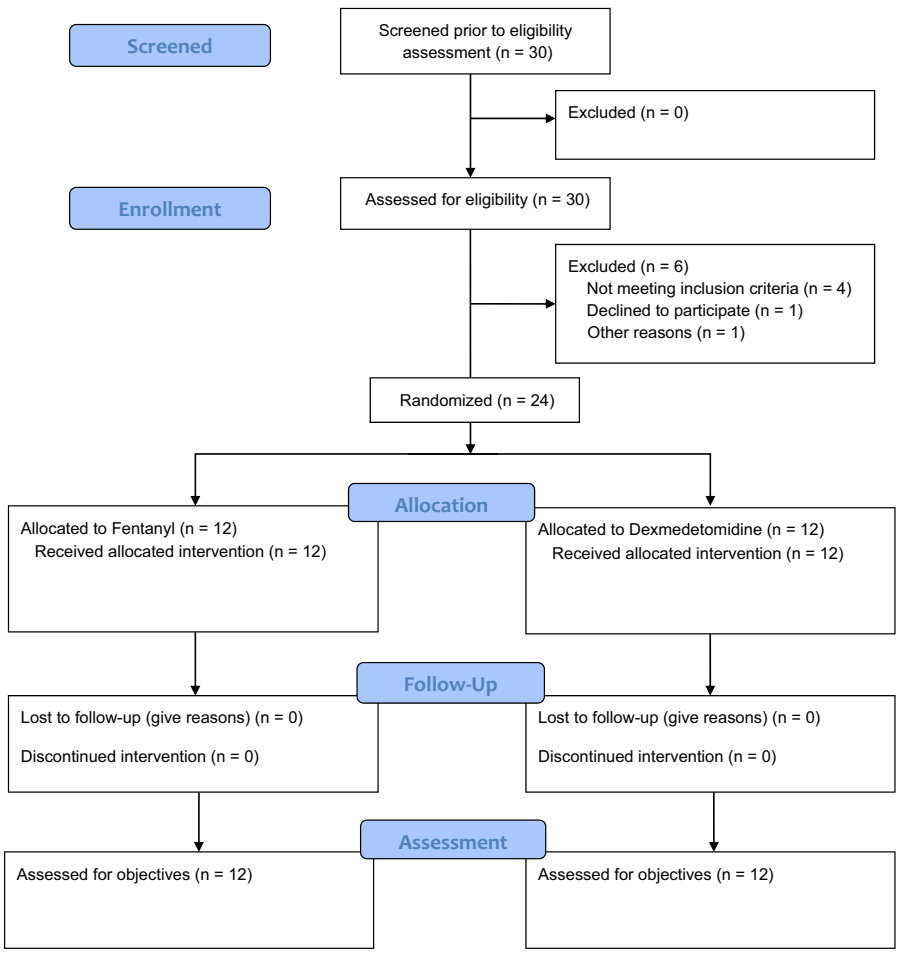

FIGURE 1 CONSORT flow diagram depicting flow of patients into the study

TABLE 1 Demographic and clinical characteristics of patients

Variable	Fentanyl (n = 12)	Dexmedetomidine (n = 12)	*P* value
Age (y)	42.3 (14.8)	42.9 (11.3)	0.914
Weight (kg)	62.9 (9.8)	63.4 (13.8)	0.919
Gender (Male)	6 (50)	8 (66.7)	0.680
Surgery duration (min)	185 (171.25-216.25)	197 (165-277.5)	0.773
Anaesthesia duration (min)	240 (226.25-270)	237 (221.25-311.25)	0.685
Study drug infusion (min)	205.5 (178.75-248.75)	200 (181.25-281.25)	0.931
Fluid balance (mL)	1818.3 (408.6)	1668.3 (634.3)	0.498
Blood loss (mL)	375 (300-725)	425 (350-575)	0.705
Total vecuronium dose (mg)	12 (10-15.5)	10 (10-12)	0.141

Values expressed as mean (SD) or median (IQR) or n (%).
IQR, interquartile range; n, number; SD, standard deviation.

by recruiting the planned number of patients within 2 months, well ahead of our predetermined timeline of 4 months, and by 100% protocol adherence.

Our secondary outcome data of bolus fentanyl consumption and NRS scores were not normally distributed. Hence, we used Mann-Whitney *U* test for our exploratory analyses. Additional fentanyl dose (μg) requirements measured as median and IQR, in the fentanyl and dexmedetomidine groups were 25 (0-50) and 0 (0-50) respectively; $P = 0.844$. The 95% confidence interval (CI) for the median difference between fentanyl and dexmedetomidine medians was (0, 50) using Hodges-Lehmann estimation. The upper margin of CI was within the defined non-inferiority margin of 100. Six and five of the 12 patients in the fentanyl and dexmedetomidine groups respectively required at least one 50 μg bolus of fentanyl ($^{x2} = 0.168$; $P = 1.000$). The NRS at 15 minutes was 0 in both the groups. The additional fentanyl dose and the NRS scores at 60 minutes, 24 and 48 hours are shown in Table 2. No patient received postoperative opioids for pain management.

The number of episodes of hypotension and hypertension was similar in both the groups. (Table 3) In all patients, hypotension episodes responded to 1-2 bolus doses of 6 mg mephentermine and no patient required vasopressor infusion. Hypertensive episodes responded to fentanyl boluses. No patient developed significant bradycardia. All episodes of hypertension except one were associated with tachycardia. No patient in either group developed respiratory depression or pruritis.

Five patients in the fentanyl group and four in the dexmedetomidine group had RASS score of ≤−2 while one patient in the fentanyl and none in the dexmedetomidine group had RASS score ≥+2 at extubation. There was no difference between the groups regarding time for extubation and verbal response or haemodynamics at extubation. (Table 3) Three patients in the fentanyl group and six in the dexmedetomidine group had coughing at extubation.

TABLE 2 Total bolus fentanyl consumption and postoperative numerical rating scale (NRS)

Variable	Fentanyl (n = 12)	Dexmedetomidine (n = 12)	*P* value
Additional fentanyl dose (μg)	25 (0-50)	0 (0-50)	0.844
NRS 60 min after surgery	0.5 (0.0-3.0)	0.0 (0.0-1.75)	0.415
NRS 24 h after surgery	3 (3-3.5)	3 (0-7.5)	0.571
NRS 48 h after surgery	2 (0-3)	2 (1.5-4)	0.153

Values expressed as median (interquartile range).

4 | DISCUSSION

4.1 | Summary of findings

We achieved a high recruitment rate (80%) and protocol adherence rate (100%) indicating feasibility of conducting a larger trial examining efficacy and harms of dexmedetomidine as an alternative intraoperative analgesic to fentanyl during craniotomies. In this pilot study, the bolus fentanyl requirement during the surgery was within the non-inferiority margin of 100 μg suggesting that dexmedetomidine is potentially non-inferior to fentanyl for intraoperative analgesia. Studies have shown that despite multimodal analgesia including scalp block, craniotomy patients may need intraoperative opioid supplementation. In a recent review looking at opioid free analgesia for supratentorial craniotomies, we found only five small studies using completely non-opioid modalities, with no consistent findings.[15] Although fentanyl and dexmedetomidine have short half-lives, it is likely that they potentiate and contribute to effective multimodal postoperative analgesia as demonstrated by low NRS pain scores

TABLE 3 Adverse events and recovery characteristics

Variable	Fentanyl (n = 12)	Dexmedetomidine (n = 12)
Intraoperative hypotension ≥2 episodes	5 (42%)	5 (42%)
Intraoperative hypertension ≥1 episode	5 (42%)	5 (42%)
Postoperative nausea vomiting	2 (17%)	0 (0%)
Shivering in postanaesthesia care unit	1 (8%)	0 (0%)
Time to extubation (min)	9.00 (4.00-16.25)	7.50 (4.25-12.75)
Time to verbal response (min)	14.00 (7.50-25.00)	14 (7.50-19.75)
Heart rate at extubation (bpm)	97.50 (91.00-104.75)	95.00 (90.50-100.75)
Mean blood pressure at extubation (mmHg)	100.00 (82.00-110.75)	105.50 (100.00-114.50)

Values expressed as n (%) or median (interquartile range).

in both the groups in the PACU and on the first two postoperative days.[16] In our study no patient required administration of opioids in the postoperative period. No patient in either group developed any significant complication related to the study drug. The quality of recovery was also similar in both the groups.

4.2 | Comparison with previous literature

The only study evaluating remifentanil with dexmedetomidine for perioperative analgesia during neurosurgery did not evaluate intraoperative opioid requirements and postoperative pain scores, thereby making it difficult to compare with our study.[10] Many earlier studies having dexmedetomidine in the anaesthetic regimen used it as a co-analgesic rather than as a sole analgesic.[7-9] In non-craniotomy surgeries, non-opioid intravenous techniques have shown similar analgesic effects with fewer complications.[4-6] Most studies evaluating the use of dexmedetomidine for analgesia have compared postoperative pain and analgesic requirements and showed benefits of the medication lasting up to 24 or 48 hours. Bielka et al observed reduced postoperative morphine consumption, prolonged time to rescue analgesia till 24 hours and fewer patients with severe postoperative pain after laparoscopic cholecystectomy in patients receiving intraoperative dexmedetomidine 0.5 $\mu g\, kg^{-1}\, h^{-1}$ as compared to normal saline infusion.[16] Gurbet et al observed a reduction in postoperative opioid consumption with dexmedetomidine infusion vis-à-vis saline infusion without any difference in the pain scores after abdominal hysterectomy.[17] However, no such differences in either the pain scores or opioid consumption were observed by Naik et al who compared dexmedetomidine and saline in their study on 142 patients having major spine surgery. In fact, the study was terminated after an interim analysis for futility as the estimated sample size was insufficient to show a difference in opioid consumption postoperatively. Interestingly, this study also compared the intraoperative opioid requirements, administered as fentanyl boluses similar to our study, and observed a statistically significant decrease by 50%: median [IQR] of 3.5 [0-11] versus 7 [3-15] in dexmedetomidine versus saline group, respectively, $P = 0.04$.[18] It is likely that differences in patient population impacts the effects of dexmedetomidine on postoperative analgesia apart from possible study related differences due to sample size and bias.

4.3 | Strengths and limitations

This is the first study attempting to assess the use of dexmedetomidine as an alternative to opioids for perioperative analgesia in craniotomy patients. This study is timely and critical, as we look out for opioid free analgesic modalities and to avoid immediate opioid related side effects.

However, being a pilot study, we cannot draw clinical conclusions based on our result. Use of non-inferiority designs can also have inherent limitations such as no internal demonstration of assay sensitivity, lack of single conservative analysis approach, and difficulty in specifying the non-inferiority margin.[19] Our non-inferiority margin of 0-100 μg can be considered appropriate as Naik et al observed that a median dose of 350 μg of fentanyl was used in their study comparing dexmedetomidine versus saline.[18] Another study also observed a median difference in intraoperative fentanyl requirement of 150 μg to be non-inferior between paravertebral block with propofol group and general anaesthesia group.[20]

5 | CONCLUSIONS

Our study demonstrates that comparison of dexmedetomidine with fentanyl for perioperative analgesia is feasible for craniotomies and dexmedetomidine demonstrates a potentially non-inferior effect to fentanyl for intraoperative opioid requirement, postoperative pain scores and perioperative adverse events. A larger trial adapting this study design is essential to inform clinical decision-making and routine use of dexmedetomidine as an alternative to opioids for perioperative analgesia in craniotomies.

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DISCLOSURE

None.

ORCID

Kamath Sriganesh https://orcid.org/0000-0003-2355-0403

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CHAPTER 7

OPIOID VERSUS NON-OPIOID ANALGESIA FOR CRANIOTOMY: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Sriganesh K, Bharadwaj S, Shanthanna H, Rao GSU, Kramer BW, Sathyaprabha TN

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Opioid versus Nonopioid Analgesia for Craniotomy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Kamath Sriganesh[1], Suparna Bharadwaj[1], Harsha Shanthanna[2], Ganne S. Umamaheswara Rao[1], Boris W. Kramer[3,4], Talakad N. Sathyaprabha[1]

■ BACKGROUND: **Despite the use of intraoperative opioid analgesia, postoperative pain is often reported by patients undergoing craniotomies. Opioids also cause undesirable side effects in neurosurgical patients. Hence, the role of nonopioid analgesia has been explored for craniotomies in recent years.**

■ METHODS: **This systematic review evaluated evidence from randomized controlled trials (RCTs) comparing opioid and nonopioid analgesia during craniotomies regarding postoperative pain, recovery, and adverse events.**

■ RESULTS: **Of the 10,459 records obtained by searching MEDLINE, Embase, and Web of Science databases, 6 RCTs were included. No difference was observed in pain scores between opioid and nonopioid analgesia at 1 and 24 hours after surgery: mean difference (MD), 1.11 units; 95% confidence interval [CI], −0.16 to 2.38, *P* = 0.09 and MD, −0.06 units; 95% CI, −1.14 to 1.01, *P* = 0.91, respectively. The time for first postoperative analgesic requirement was shorter with opioids but was not statistically significant (MD, −84.77 minutes; 95% CI, −254.65 to 85.11; *P* = 0.33). Postoperative nausea and vomiting (relative risk = 1.60; 95% CI, 0.96–2.66; *P* = 0.07) was similar but shivering (relative risk = 2.01; 95% CI, 1.09–3.71; *P* = 0.03) was greater in the opioid group than nonopioid group.**

■ CONCLUSIONS: **There were no important differences in clinical outcomes between the groups in our review. The GRADE certainty of evidence was rated low for most outcomes. Available evidence does not suggest superiority of intraoperative nonopioid over opioid analgesia for postoperative pain in patients undergoing craniotomy. More studies are needed to firmly establish the role of nonopioid intraoperative analgesics as an alternative to opioids in this population.**

INTRODUCTION

The selection of analgesic agents during surgery can influence postoperative pain and analgesic requirements. Opioids such as fentanyl, morphine, and remifentanil are the most common analgesics used to reduce nociceptive response and anesthetic needs during surgery.[1] Despite their liberal use, pain is often reported by patients after craniotomy.[2,3] Moreover, opioid side effects such as miosis, respiratory depression, sedation, shivering, postoperative nausea and vomiting (PONV), and pruritis are common but undesirable in patients undergoing intracranial surgery.[4] A multimodal nonopioid analgesia strategy for craniotomies potentially including scalp block, paracetamol, and dexmedetomidine could lead to total opioid avoidance.[5]

Key words
- Craniotomy
- Nonopioid analgesia
- Opioids
- Postoperative pain
- Systematic review

Abbreviations and Acronyms
CI: Confidence interval
HR: Heart rate
MBP: Mean blood pressure
MD: Mean difference
PACU: Postanesthesia care unit
PONV: Postoperative nausea and vomiting
RCT: Randomized controlled trial
RoB: Risk of bias
RR: Risk ratio

From the [1]National Institute of Mental Health and Neurosciences, Bengaluru, India; [2]Department of Anesthesia, McMaster University, Hamilton, Ontario, Canada; [3]Maastricht University Medical Center, The Netherlands; and School of Women's and Infants' Health, University of Western Australia, Australia

To whom correspondence should be addressed: Kamath Sriganesh, D.M. [E-mail: drsri23@gmail.com]

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Previous randomized controlled trials (RCTs) comparing intraoperative opioids with nonopioid analgesia techniques for postoperative pain involved a small number of patients. Moreover, these studies reported conflicting findings, with some favoring opioids and others supporting nonopioid intraoperative analgesia regarding postoperative pain. These inconsistencies render clinical decision making a challenge in day-to-day practice regarding selection of the best intraoperative analgesia technique in patients undergoing craniotomy. Hence, there is a need to perform meta-analysis of these RCTs to understand the overall effect and magnitude of effect on postoperative pain scores and to understand if the individual studies are representative or an exception to the general rule about nonopioids as an alternative to opioids for perioperative analgesia management in patients undergoing craniotomy.

This systematic review and meta-analysis aimed to identify RCTs comparing intraoperative nonopioid analgesia with opioid analgesia in patients undergoing craniotomy. The objectives of this review were to identify trials comparing opioid with nonopioid analgesia and provide pooled estimates of effect for postoperative pain scores at 1 and 24 hours after craniotomy, recovery characteristics (time to extubation and response to verbal commands, periextubation heart rate [HR] and mean blood pressure [MBP], and time to discharge from postanesthesia care unit [PACU]) and adverse events (PONV, shivering, sedation, pruritis, and respiratory depression).

METHODS

This review is registered with PROSPERO (International Prospective Register of Systematic Reviews) (CRD42020209042 dated October 14, 2020).[6] The manuscript has been prepared as per the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Eligibility Criteria

We included RCTs if they compared opioid with nonopioid analgesia in the intraoperative period in adult patients (>18 years) undergoing craniotomy and if the study groups had received a similar anesthesia technique. Studies were included if only a single dose of short-acting opioid was used during anesthetic induction to ablate nociceptive response to laryngoscopy and intubation in both groups. No restrictions were applied at the initial search stage. Studies were excluded if they were other than RCTs, involved children or noncraniotomy surgery, RCTs comparing opioids with nonopioids in the postoperative period, and if they did not report pain outcomes.

Information Sources

Electronic databases of MEDLINE, Embase, and Web of Science were searched from their inception until March 19, 2022. Additional strategies to identify studies included manual reviews of reference lists from articles that fulfilled our eligibility criteria and use of the "related articles" feature in PubMed.

Search Strategy

An experienced librarian in discussion with the first author performed the literature search for 3 databases. We included terms referring to our study population of patients undergoing craniotomy and study interventions and comparators involving any opioid and nonopioid drugs for analgesia during surgery. The search strategy for each database is provided as a supplementary file (**Supplementary Appendix 1**).

Study Selection

Two reviewers (K.S. and S.B.) independently screened the articles for selection in 2 stages. A calibration exercise was performed at the beginning to ensure consistency in screening and selection. Titles and abstracts were screened using Rayyan (http://rayyan.qcri.org) in the first stage, and full-text screening was undertaken in the second stage. Disagreements were addressed by consensus between the 2 reviewers and if persistent, were settled by a senior author. The interobserver agreement on full-text selection was assessed using a quadratic κ statistic.[7]

Data Extraction

Data were extracted from the included studies by the same 2 reviewers independently and in duplicate, using a Microsoft Excel worksheet (Microsoft, Redmond, Washington, USA) after an initial piloting exercise for consistency and accuracy. An instruction sheet provided guidance about the data extraction process. Data regarding study characteristics, interventions and comparators, patient characteristics, definitions of pain, pain scales used and time of assessments, outcomes as continuous or binary measures and their time points of assessments, and potential risk of bias (RoB) items were extracted. Individual study authors were contacted by e-mail to obtain missing data or to clarify unclear items essential for the review.

RoB

The RoB of each study was assessed independently by the same reviewers using the Cochrane RoB tool 2 for RCTs. This process helped capture components of potential bias arising from randomization, bias caused by deviations from intended interventions, bias caused by missing outcome data, bias in measurement of outcome, and bias in selection of reported result.[8] The RoB was categorized as low, some concerns, and high. Study authors were not contacted to clarify RoB items and discrepancies were resolved through consensus. If the outcomes described in the Methods section were not reported in the Results section, bias in selection of the reported result was considered.

Outcome Assessments and Time Points

The predetermined primary outcome of this review was severity of postoperative pain reported using a pain score. Other outcomes included postoperative opioid consumption until 24 hours after craniotomy, time for the first administration of rescue analgesia, adverse events related to the study drugs, and characteristics of recovery from anesthesia (time to extubation and response to verbal commands, periextubation HR and MBP, and time to discharge from the PACU). Pain outcome details were extracted as reported by authors in primary studies (pain score used, reporting of pain as continuous and categorical outcomes, and time points of assessment). The most commonly used time points of 1 and 24 hours after surgery were used for meta-analysis of postoperative

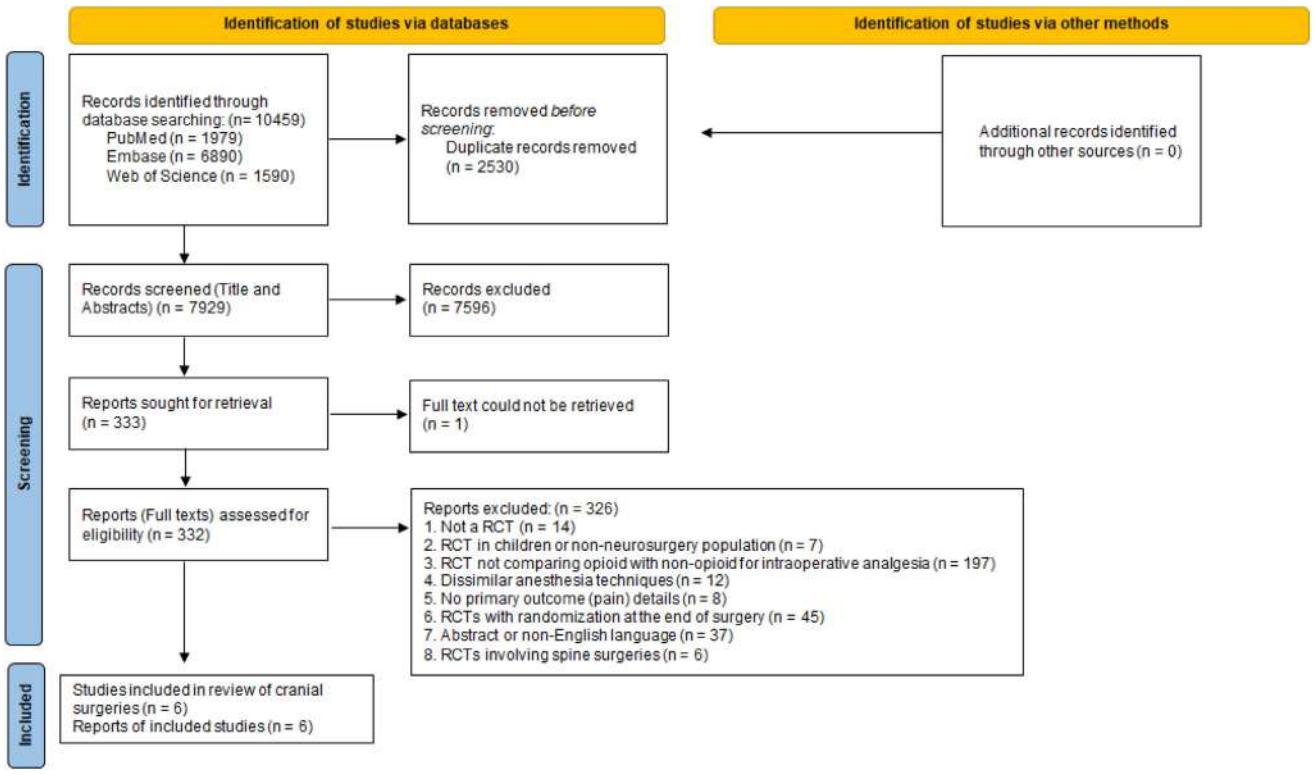

Figure 1. PRISMA flow diagram showing records after database search. RCT, randomized controlled trial.

pain scores. We planned to transform pain scores to the most commonly used and easily interpretable 0–10 scale (0, no pain; 10, severe pain), if the primary studies reported the pain scores.[9] The adverse events (PONV, pruritis, sedation, shivering, and respiratory depression) were evaluated by comparing their occurrence in the opioid and nonopioid groups. The most commonly reported time points were considered for pooling of the outcome results if there were multiple time points reported.

Synthesis of Results and Summary Measures

The extracted and compiled data were checked for accuracy using Microsoft Excel. The data analysis and synthesis were performed using Review Manager (RevMan version 5.4.1; https://training.cochrane.org/online-learning/core-software/revman) 2020. Meta-analysis was performed only when there were at least 2 studies for a particular outcome. A random-effects model (inverse variance statistical method) was used for the meta-analysis. The risk ratio (RR) was estimated for dichotomous outcomes and mean difference (MD) for continuous outcomes with their 95% confidence interval (CI). A Cochran Q test was used to estimate statistical heterogeneity with a threshold of $P = 0.1$, and percentage variability in individual effect estimates was described with the I^2 statistic. The certainty of evidence was rated using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach,[10] with a table to summarize the findings.

RESULTS

Study Selection

The search of 3 databases retrieved 10,459 articles as of 19 March 2022 (updated search results). After removal of duplicates, 7929 records were available for screening. The review of titles and abstracts of these articles resulted in 333 records being eligible for full-text assessment. Full text was not available for 1 study.[11] Following full-text review, 5 studies were selected for inclusion, as shown in the PRISMA 2020 flow diagram (**Figure 1**). A substantial agreement ($\kappa = 0.76$) between the 2 reviewers was noted for full-text assessment.

Study Characteristics

The individual study characteristics such as duration of surgery, age, sex, opioid and nonopioid drugs used, pain outcome assessed, and follow-up period after surgery are shown in **Table 1**. Remifentanil[13,15,17] and fentanyl[12,14,16] were the intraoperative opioid analgesics used in 3 studies each, whereas dexmedetomidine was the intraoperative nonopioid intervention in all studies[13-17] except one,[12] in which scalp block was used.

Table 1. Characteristics of Included Studies: Population, Intervention, Comparator, Outcome, and Study Duration

Sl Number	Reference, Population, Total Number of Patients	Surgery Duration (minutes)		Age (years), Mean (Standard Deviation)		Male Gender (n/Total)		Intervention	Comparator	Primary Pain Outcome Assessed	Follow-Up Period
		Opioid	Nonopioid	Opioid	Nonopioid	Opioid	Nonopioid	Opioid (Route)	Nonopioid (Route)		
1	Biswas and Bithal, 2003[12]	223.9 (7)	196 (36.5)	34.0 (10.5)	32.0 (9.5)	10/20	14/21	Fentanyl (IV)	Bupivacaine (SB)	Postoperative pain score	48 hours
	Supratentorial craniotomy, 41										
2	Gunduz et al., 2009[13]	239.6 (93.8)	242.4 (83)	41.2 (12.3)	48.1 (12.5)	25/40	23/40	Remifentanil (IV)	Dexmedetomidine (IV)	24 hours analgesic requirement	24 hours
	Supratentorial craniotomy, 80										
3	Gupta et al., 2017[14]	103.52 (9.51)	105.96 (9.53)	39.7 (14.5)	42.8 (13.8)	11/25	14/25	Fentanyl (IV)	Dexmedetomidine (IV)	Postoperative pain (score not informed)	24 hours
	Supratentorial craniotomy, 50										
4	Rajan et al., 2016[15]	228 (90)	210 (78)	55.0 (14.0)	56.0 (14.0)	34/71	35/68	Remifentanil (IV)	Dexmedetomidine (IV)	Postoperative pain score	90 minutes
	Craniotomy/transsphenoidal surgery, 139										
5	Sriganesh et al., 2019[16]	210.92 (68.48)	216.17 (60.34)	42.3 (14.8)	42.9 (11.3)	6/12	8/12	Fentanyl (IV)	Dexmedetomidine (IV)	Postoperative pain score	48 hours
	Supratentorial craniotomy, 24										
6	Turgut et al., 2009[17]	229.4 (37.06)	216.08 (52.01)	53.6 (10.1)	56.5 (12.5)	NA	NA	Remifentanil (IV)	Dexmedetomidine (IV)	Time to first analgesic requirement	120 minutes
	Supratentorial craniotomy, 50										

IV, intravenous; NA, not available; Sl, serial number; SB, scalp block.

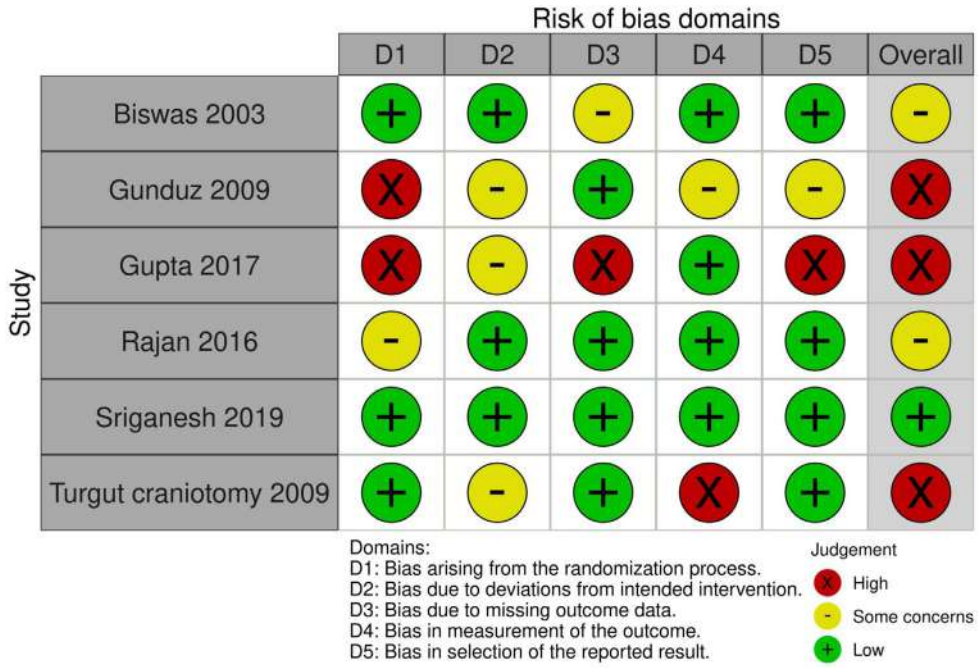

Figure 2. Potential risk of bias of included studies.

RoB

The potential RoB was high for 2 studies based on the randomization process, high or some concerns for bias because of missing outcome data, bias in measurement of the outcome, and bias in selection of the reported results for 1 study each, and low or some concerns for bias because of deviations from intended interventions for 1 study. Figure 2 shows the potential RoB of the included studies.

Study Outcomes

Three of the 6 included studies[12,15,16] reported postoperative pain scores using a 0–10 scale, 1 study[17] reported time to first analgesic requirement, and another[13] reported opioid consumption in the first 24 hours after surgery as the primary pain outcome. One study[14] did not report pain outcome in the results although it was mentioned as assessed in the Methods section. The time points of postoperative pain assessments varied from immediately after extubation to 48 hours after craniotomy, with pain scores available at 1 and 24 hours after surgery for 3 and 2 studies, respectively. Four studies reported PONV and shivering as the adverse events.[14-17] Except for 1 study,[12] the rest reported at least 1 recovery outcome.

Compared with the nonopioid group ($n = 101$), the opioid group ($n = 103$) had a higher pain score at 1 hour after craniotomy, but this was not statistically significant: 3 studies, MD, 1.11 units; 95% CI, −0.16 to 2.38, $I^2 = 45\%$, $P = 0.09$ (Figure 3A). Similarly, there was no difference in pain score between the 2 groups at 24 hours after surgery: 2 studies, MD, −0.06 units; 95% CI, −1.14 to 1.01, $I^2 = 0\%$, $P = 0.91$ (Figure 3B). The time for first postoperative analgesia requirement was shorter (but statistically insignificant) for the opioid ($n = 45$) group compared with the nonopioid ($n = 46$) group: 2 studies, MD, −84.77 minutes; 95% CI, −254.65 to 85.11, $I^2 = 92\%$, $P = 0.33$ (Figure 3C).

The adverse events reported in the included studies were PONV ($n = 5$), shivering ($n = 5$), sedation ($n = 1$), pruritis ($n = 1$) and respiratory depression ($n = 1$). The incidence of PONV was similar in the opioid ($n = 133$) and nonopioid groups ($n = 130$) (RR, 1.60; 95% CI, 0.96–2.66; $I^2 = 0\%$; $P = 0.07$) (Figure 4A). However, the incidence of postoperative shivering was significantly higher in the opioid group compared with the nonopioid group (RR, 2.01; 95% CI, 1.09–3.71; $I^2 = 0\%$; $P = 0.03$) (Figure 4B). No meta-analysis was possible for other adverse events because fewer than 2 studies reported them.

The recovery characteristics between opioid and nonopioid groups were reported as time to respond to verbal commands ($n = 5$), time to extubation after discontinuation of anesthesia ($n = 4$), PACU discharge time ($n = 2$), and periextubation HR ($n = 4$) and MBP ($n = 4$). The time to extubation and to respond to verbal commands were similar for opioid and nonopioid analgesia groups (MD, −0.14 minutes; 95% CI, −2.39 to 2.11; $I^2 = 86\%$; $P = 0.90$) and (MD, −6.34 minutes; 95% CI, −15.19 to 2.50; $I^2 = 99\%$; $P = 0.16$) (Figure 5A and B). Similarly, there was no difference between the opioid and nonopioid groups regarding periextubation HR and MBP (MD, 4.62 beats per minutes; 95% CI, −5.33 to 14.57; $I^2 = 91\%$; $P = 0.36$) and (MD, 7.21 mm Hg; 95% CI, −1.34 to 15.76; $I^2 = 94\%$; $P = 0.10$) (Figure 5C and D). The time to discharge from PACU was also similar in patients receiving opioid and nonopioid analgesia during surgery (MD, −2.37 minutes; 95% CI, −4.91 to 0.17; $I^2 = 0\%$; $P = 0.07$) (Figure 5E).

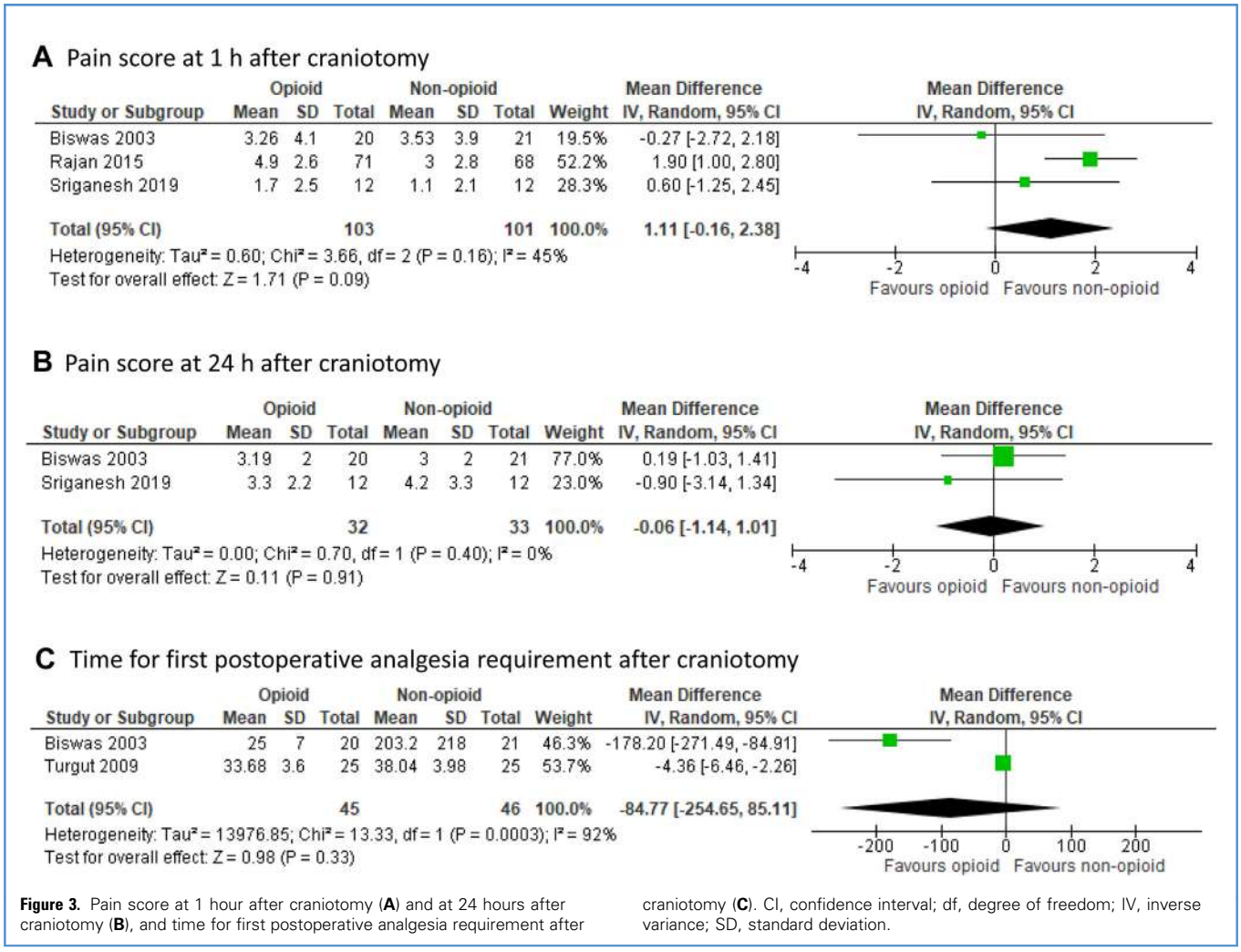

Figure 3. Pain score at 1 hour after craniotomy (**A**) and at 24 hours after craniotomy (**B**), and time for first postoperative analgesia requirement after craniotomy (**C**). CI, confidence interval; df, degree of freedom; IV, inverse variance; SD, standard deviation.

The GRADE certainty of evidence was evaluated for study outcomes using GRADEpro GDT software[18] and is presented in Supplementary Appendix 2. The certainty of evidence was very low for pain scores, low to moderate for adverse events (PONV and shivering), and low to very low for recovery outcomes (extubation and awakening times). These results were mainly caused by RoB and inconsistency or imprecision for the outcome measures.

Publication Bias

Publication bias assessed for the primary outcome (postoperative pain) using funnel plots and Egger test indicated no bias (Supplementary Appendix 3A and B).

DISCUSSION

Summary of Findings

In this systematic review and meta-analysis of patients who underwent craniotomy, postoperative pain scores at 1 and 24 hours after surgery were similar with intraoperative use of either opioid or nonopioid analgesia. Similarly, there was no difference in the time for the first analgesic requirement after craniotomy. Postoperative shivering was less in the nonopioid analgesia group, whereas PONV incidence was similar to that in the opioid analgesia group. There was no difference in the recovery characteristics (time to extubation and response to verbal commands, periextubation HR and MBP, and time to discharge from PACU) between the opioid and nonopioid analgesia groups.

Review of Literature

Most patients undergoing craniotomy experience moderate to severe pain for the first 2 days after surgery.[19] Postoperative pain occurs despite the use of potent opioids during the intraoperative period. Moreover, although undesirable, opioid-related side effects are common in patients undergoing craniotomy. To overcome these limitations, studies have evaluated the role of nonopioid analgesia either alone or as a combination with opioids in patients undergoing craniotomy. However, there are

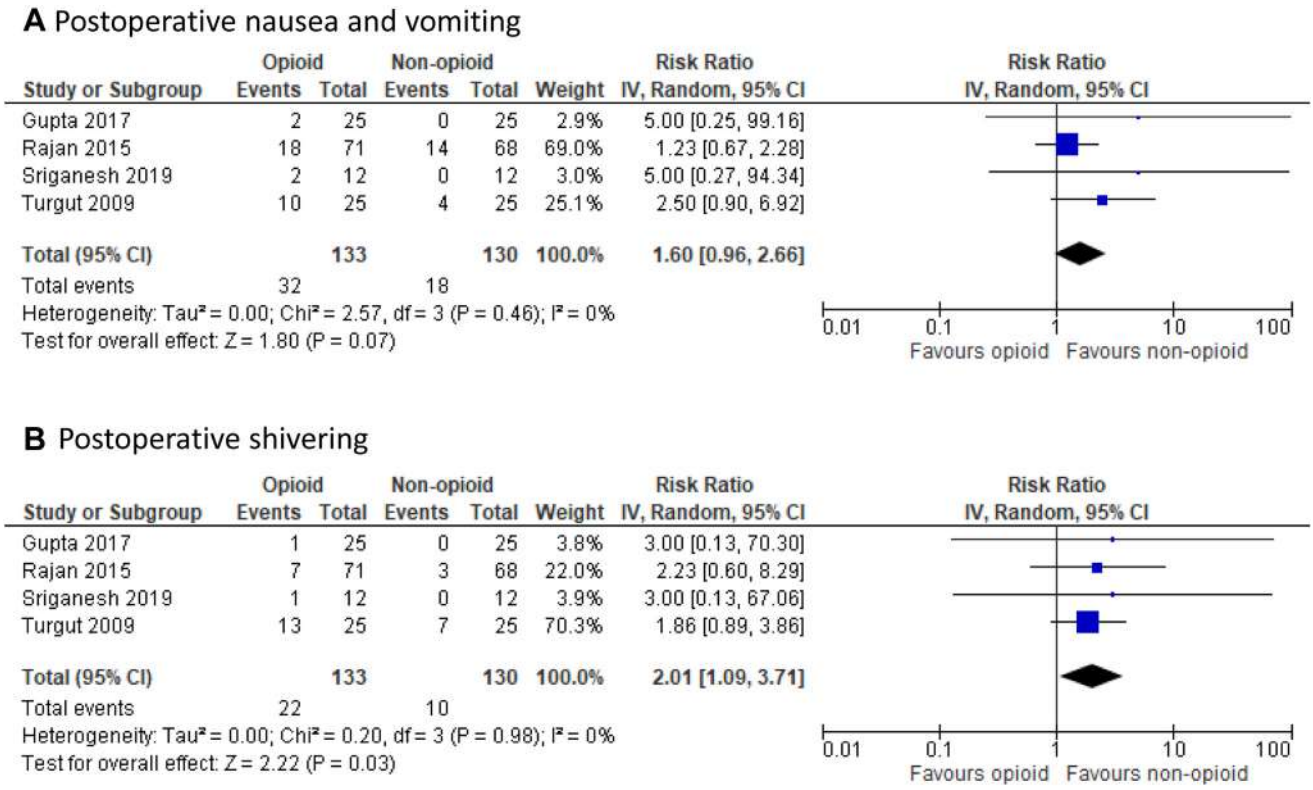

Figure 4. Comparison of postoperative nausea and vomiting (**A**) and comparison of postoperative shivering (**B**). CI, confidence interval; df, degree of freedom; IV, inverse variance; SD, standard deviation.

only a few RCTs making one-to-one comparison of intraoperative opioids and nonopioid analgesics for pain management in patients undergoing craniotomy.[11-17] The results of these individual trials conflict with a study[12] observing lower postoperative pain score at 1 hour after surgery with intraoperative opioid analgesia, whereas other studies[15,16] have noted higher pain scores with opioid analgesia. Similarly, inconsistent findings were observed for postoperative pain scores at 24 hours after surgery, with one study reporting lower[16] and another study reporting higher[12] pain scores with intraoperative opioid analgesia compared with nonopioid analgesia. Our pooled results from these trials suggest that both techniques provide similar postoperative pain relief when used for intraoperative analgesia.

Fentanyl and remifentanil were the opioids used in the studies included in this review, whereas dexmedetomidine was the most common nonopioid analgesic. Although remifentanil is an ultrashort-acting analgesic, the effects of dexmedetomidine last beyond the duration of infusion.[20] However, superiority of intraoperatively administered nonopioid analgesia over opioid analgesia was not observed in this review for postoperative pain, recovery profile, or adverse events except shivering. Because opioids are primary intraoperative analgesics for craniotomies in most places, a change in clinical practice to use only nonopioids cannot be suggested based on our review. In this review, we included only those studies that reported using nonopioid analgesia intervention (dexmedetomidine or scalp block) as the sole or primary technique in the nonopioid group and compared with an opioid (fentanyl or remifentanil). However, many studies reported using acetaminophen,[16] nonsteroidal antiinflammatory drugs,[14] or tramadol[13,17] toward the end of surgery to provide postoperative analgesia in both the groups.

Fear of opioid side effects can lead to undertreatment of pain in patients undergoing brain surgery. Although not captured as part of our review, clinically the use of multimodal analgesia incorporating nonopioid strategies such as scalp block, dexmedetomidine, gabapentinoids, and nonsteroidal antiinflammatory drugs in appropriate combinations would likely be the most pragmatic approach and can be expected to lead to significant opioid sparing as well.[5,21-24]

Limitations

This review included only those studies that compared opioid and nonopioid intraoperative analgesia in patients who underwent craniotomy. However, the included studies had disparities in reporting of the time of assessments of pain and type of opioid and nonopioid analgesics used. Two studies reported using nitrous oxide during surgery in both opioid and nonopioid arms.

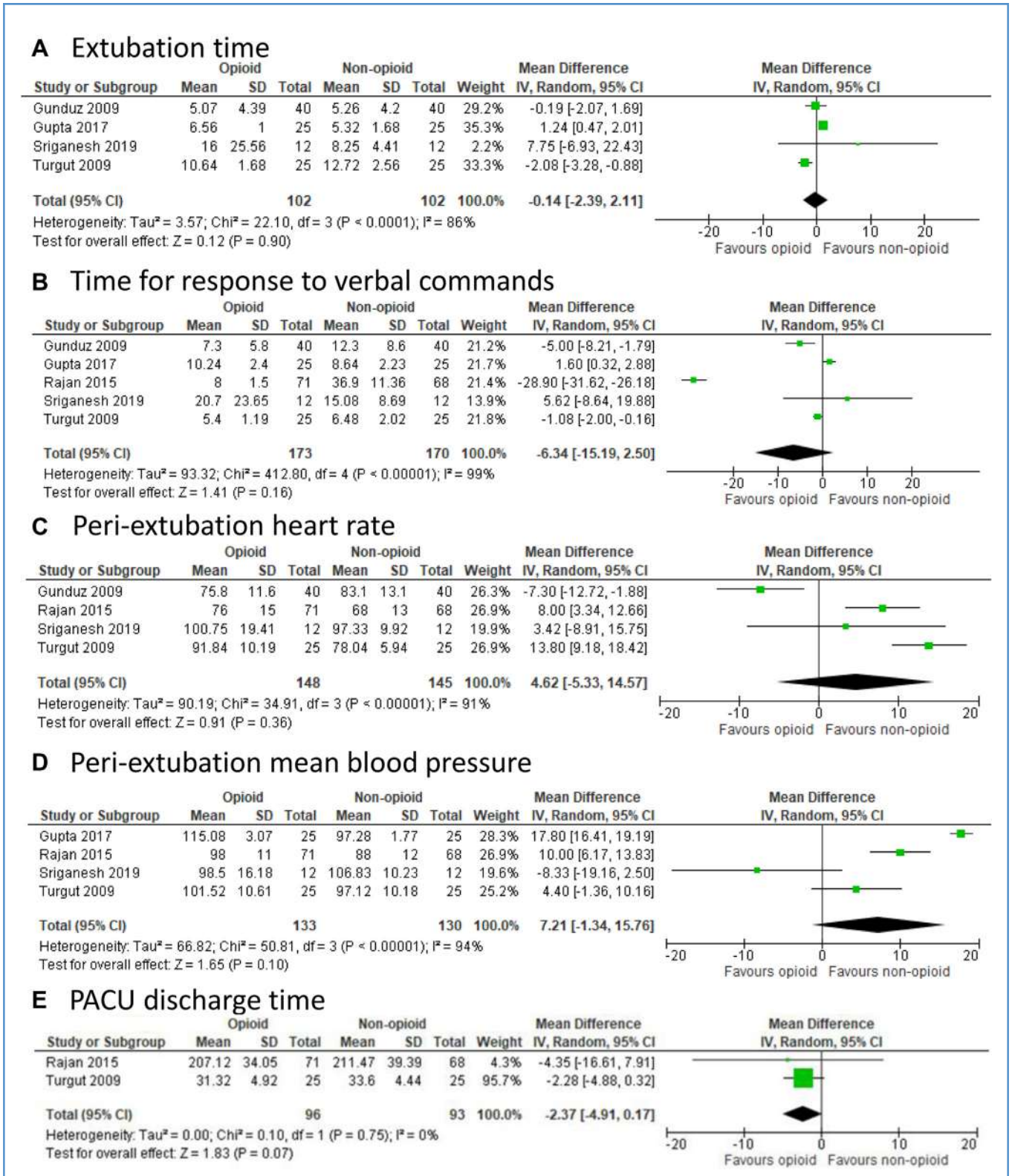

Figure 5. Time to extubation after surgery (**A**), time to respond to verbal commands (**B**), comparison of periextubation heart rate (**C**), comparison of periextubation mean blood pressure (**D**), and comparison of discharge time from the postanesthesia care unit (**E**). CI, confidence interval; df, degree of freedom; IV, inverse variance; SD, standard deviation.

Four of the 6 included studies reported using bolus opioid in both the groups at anesthetic induction to ablate nociceptive response to laryngoscopy and intubation before randomization to study interventions. The residual effect of fentanyl at induction could influence postoperative pain, although this is unlikely because the duration of action of fentanyl is between 30 and 60 minutes.[25] No meta-analysis could be performed for adverse events such as pruritis, respiratory depression, and sedation because these were reported by fewer than 2 studies. Significant heterogeneity was noted for some outcomes probably because of small sample size or few events in the RCTs. This review is limited by the quality of included studies. Therefore, there is a need for more research including good-quality primary RCTs to overcome the limitations and bring certainty to the opioid versus nonopioid analgesia debate for craniotomies.

CONCLUSIONS

Use of intraoperative opioid resulted in similar postoperative pain scores, recovery profile, and adverse events (except shivering) compared with nonopioid analgesia in patients who underwent craniotomy. The high RoB and significant heterogeneity among the included studies resulted in low to very low certainty of evidence on GRADE assessment for the study outcomes. The available evidence does not support intraoperative use of nonopioid over opioid analgesia for postoperative pain in patients undergoing craniotomy. More evidence from good-quality primary RCTs is required before considering a change in current opioid-based analgesia practice for craniotomies.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Kamath Sriganesh: Conceptualization, Methodology, Title/abstract, Full text screening and data extraction, Writing — original draft, Writing — review & editing, Final approval before submission. **Suparna Bharadwaj:** Title/abstract, Full text screening and data extraction, Writing — review & editing, Final approval before submission. **Harsha Shanthanna:** Methodology, Writing — review & editing, Final approval before submission. **Ganne S. Umamaheswara Rao:** Writing — review & editing, Final approval before submission. **Boris W. Kramer:** Conceptualization, Methodology, Writing — review & editing, Final approval before submission. **Talakad N. Sathyaprabha:** Writing — review & editing, Final approval before submission.

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CHAPTER 8

OPIOID VERSUS NON-OPIOID ANALGESIA FOR SPINE SURGERY: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Sriganesh K, Bharadwaj S, Shanthanna H, Rao GSU, Kramer BW, Sathyaprabha TN.

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REVIEW ARTICLE

Opioid versus non-opioid analgesia for spine surgery: a systematic review and meta-analysis of randomized controlled trials

Kamath Sriganesh[1] · Suparna Bharadwaj[1] · Harsha Shanthanna[2] · Ganne S. Umamaheswara Rao[1] · Boris W. Kramer[3] · Talakad N. Sathyaprabha[1,4]

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Abstract

Purpose Opioids are the primary analgesics used in patients undergoing spine surgery. Postoperative pain is common despite their liberal use and so are opioid-associated side effects. Non-opioid analgesics are gaining popularity as alternative to opioids in spine surgery.

Methods This systematic review evaluated current evidence regarding opioid and non-opioid intraoperative analgesia and their influence on immediate postoperative pain and adverse events in spine surgery.

Results A total of 10,459 records were obtained by searching Medline, EMBASE and Web of Science databases and six randomized controlled trials were included. Differences in postoperative pain scores between opioid and non-opioid groups were not significant at 1 h: 4 studies, mean difference (MD) = 0.65 units, 95% confidence intervals (CI) [−0.12 to 1.41], $p = 0.10$, but favored non-opioid at 24 h after surgery: 3 studies, MD = 0.75 units, 95%CI [0.03 to 1.46], $p = 0.04$. The time for first postoperative analgesic requirement was shorter (MD = −45.06 min, 95%CI [−72.50 to −17.62], $p = 0.001$), and morphine consumption during first 24 h after surgery was higher in opioid compared to non-opioid group (MD = 4.54 mg, 95%CI [3.26 to 5.82], $p < 0.00001$). Adverse effects of postoperative nausea and vomiting (Relative risk (RR) = 2.15, 95%CI [1.37 to 3.38], $p = 0.0009$) and shivering (RR = 2.52, 95%CI [1.08 to 5.89], $p = 0.03$) were higher and bradycardia was lower (RR = 0.35, 95%CI [0.17 to 0.71], $p = 0.004$) with opioid analgesia.

Conclusion The certainty of evidence on GRADE assessment is low for studied outcomes. Available evidence supports intraoperative non-opioid analgesia for overall postoperative pain outcomes in spine surgery. More research is needed to find the best drug combination and dosing regimen.

Prospero Registration: CRD42020209042.

Keywords Adverse events · Spine surgery · Non-opioid analgesia · Opioids · Postoperative pain · Systematic review

Introduction

Opioids are the primary analgesics used for perioperative pain management both in developed and developing world [1, 2]. However, considering their potential for abuse and undesirable side effects in patients undergoing spine surgery [3], non-opioid analgesics including loco-regional and multimodal analgesia techniques are increasingly utilized to reduce or avoid perioperative opioid administration [4–8]. Many patients undergoing spine surgery have preexisting pain and these patients continue to experience pain in the postoperative period as well [9]. For early ambulation and discharge after spine surgery, pain management strategies should begin before surgery, continue intraoperatively and extend into the postoperative period. Postoperative pain can

Kamath Sriganesh and Boris W Kramer conceptualized the study.

✉ Kamath Sriganesh
drsri23@gmail.com

1 Department of Neuroanaesthesia and Neurocritical Care, National Institute of Mental Health and Neurosciences, Neurosciences Faculty Block, 3rd Floor, Bengaluru, India

2 Department of Anesthesia, McMaster University, Hamilton, ON, Canada

3 Maastricht University Medical Center, The Netherlands, School of Women's and Infants' Health, University of Western Australia, Perth, Australia

4 Department of Neurophysiology, National Institute of Mental Health and Neurosciences, Bengaluru, India

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be minimized to a great extent with good intraoperative analgesia, yet a significant variance and bias in intraoperative pain management is seen [10]. There are limited randomized controlled trials (RCTs) which have directly compared to postoperative pain outcomes in patients undergoing spine surgery receiving intraoperative opioid analgesia versus non-opioid analgesia [11–16]. Moreover, these primary studies had small sample size to instill confidence for change in current practice.

The purpose of this systematic review was to identify RCTs comparing intraoperative administration of opioid with non-opioid analgesia in patients undergoing spine surgery and inform pooled estimates of effect for pain relief and adverse outcomes. We assessed postoperative pain scores at 1 and 24 h after surgery, time to first requirement of rescue analgesia and opioid use in the first 24 h after spine surgery as our primary objectives. Our secondary objectives were to compare adverse events related to opioid and non-opioid analgesia such as postoperative nausea and vomiting (PONV), pruritis, sedation, respiratory depression, shivering, bradycardia and hypotension and recovery characteristics of time to respond to verbal commands, peri-extubation hemodynamics and discharge time from the postanesthesia care unit (PACU).

Methods

This systematic review was registered with the PROSPERO- CRD42020209042 on 14-10-2020 [17]. This manuscript is prepared as per PRISMA guidelines [Appendix S1: PRISMA checklist].

Inclusion and exclusion criteria

We included RCTs that compared opioid with non-opioid as the primary intraoperative analgesia technique in adult patients undergoing spine surgery. Trials were included if both groups had received similar anesthesia and differed only with regard to the primary analgesics used for surgery. Included studies were allowed to use a single dose of short acting opioid for induction in both groups, considered primarily to mitigate stress response during intubation. No language or publication restrictions were applied at initial search stage. Non-RCTs, studies in children, involving non-spine surgery population, comparing postoperative opioid and non-opioid analgesia administration for pain management, where randomization was performed at the end or after the surgery, and which did not report any pain outcome were excluded for this review.

Database sources

We searched the electronic databases of Medline, EMBASE and Web of Science from their inception till March 19, 2022. We considered additional strategies to identify studies including physical reviews of reference lists from articles that fulfilled our inclusion criteria and 'related articles' option in PubMed.

Search strategy

An experienced librarian and the first author performed the literature search using a predefined strategy for all the three databases. The search terms included study population of spine surgery, study interventions and comparators involving any opioid and non-opioid drugs during surgery and any pain outcome. Our search strategy for the databases is available as an appendix [Appendix S2: Search strategy].

Study selection

Two reviewers (KS and SB) independently screened the studies for selection in two stages. A calibration exercise was performed between the reviewers to ensure consistency in screening and selection before the start of screening. Titles and abstracts were screened initially using Rayyan software tool (http://rayyan.qcri.org), following which full-text review was performed. Disagreements were addressed by consensus and if unresolved, settled by a senior author. A quadratic kappa statistic on full-text selection was estimated as a measure of inter-observer agreement [18].

Data extraction

The same pair of reviewers (KS and SB) extracted data from the included studies independently and in duplicate, using Microsoft Excel worksheet. An instruction sheet was provided to help in the data extraction process. Extracted data included study and patient characteristics, interventions and comparators, definitions, scales used and time of assessment of outcomes (continuous or binary measures) and potential Risk of Bias (RoB). We contacted individual study authors to obtain missing data or clarify items related to the study.

Risk of bias assessment

The RoB of individual studies was assessed independently by same reviewers (KS and SB) using Cochrane RoB tool

2 for RCTs. Components of potential bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result were obtained [19]. The RoB was classified as low, some concerns and high. Any discrepancies were resolved through discussion. Individual study authors were not contacted to clarify RoB items. Bias in selection of the reported result was considered if the results section did not report the outcomes described in the methods.

Outcome assessment

The primary outcome was postoperative pain score. Other outcome measures were postoperative opioid consumption during first 24 h after surgery, time for first requirement of rescue analgesia, adverse events and recovery from anesthesia (time to respond to verbal commands, peri-extubation heart rate [HR] and mean blood pressure [MBP]). Postoperative pain details were extracted as reported in the primary studies (pain score used, description of pain as continuous and categorical outcomes and time points of pain assessment). For meta-analysis, we considered the most commonly used time points of 1 and 24 h after surgery for pain scores. For pain assessment expressed as continuous scores, we transformed outcomes to a 0–10 scale, (0 = no pain, 10 = severe pain), as it is the most commonly used tool and is easy to interpret [20]. Adverse events were evaluated by comparing the risk of commonly reported adverse events—PONV, pruritis, sedation, shivering, respiratory depression, bradycardia and hypotension. When multiple time points were reported, the most commonly reported time points were considered for pooling of the outcome results.

Synthesis of results and summary measures

The extracted data were compiled using Microsoft Excel, and analysis was performed using Review Manager Software (RevMan version 5.4.1) [Computer program] The Cochrane Collaboration, 2020. Meta-analysis was performed only if there were two or more studies for an outcome domain. A random effects model (inverse variance statistical method) was used for analysis. We calculated risk ratio (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes with their 95% confidence intervals (CI). We used Cochran's Q test to estimate statistical heterogeneity and describe variability in individual effect estimates with I^2 statistic. When trials had more than two interventions, we compared data of only opioid and non-opioid group. The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach [21], with a summary of findings table.

Additional analysis

A subgroup analysis was planned if sufficient numbers of studies were available to interpret heterogeneity among studies depending on the types of intervention (non-opioid) and comparator (opioid).

Results

Study selection

Our search of the three databases retrieved 10,459 articles which after removal of duplicates resulted in 7929 records. The titles and abstracts were then screened resulting in 332 records for full-text review. Among these, 6 studies were selected after exclusion of 326 reports as noted in PRISMA 2020 flow diagram in Figure 1. A substantial agreement (kappa = 0.76) was observed for full-text assessment between the two reviewers.

Study characteristics

The study characteristics of the included studies such as surgery duration, age, gender, opioid and non-opioid drugs used, primary pain outcome and postoperative follow-up period are shown in Table 1. Three studies used remifentanil, two used fentanyl and one used morphine as the opioid intervention while five studies used dexmedetomidine and one study used ketamine as the non-opioid intervention. One study had three groups, with the third group combining opioid and non-opioid interventions [11]. In all except one study [15], the analgesic drugs were administered as intravenous infusions throughout the surgery.

Risk of bias findings

The potential RoB was high for three studies based on their randomization process and bias due to missing outcome data, some concern for one study for bias due to deviation from intended intervention and low for two studies. Figure 2 informs the potential RoB of included studies for various domains.

Study outcomes and synthesis of results

Of the included studies, three reported pain score, two reported time to first analgesic requirement and one study reported 24-h opioid consumption after surgery as their primary pain outcome. Five studies reported at least

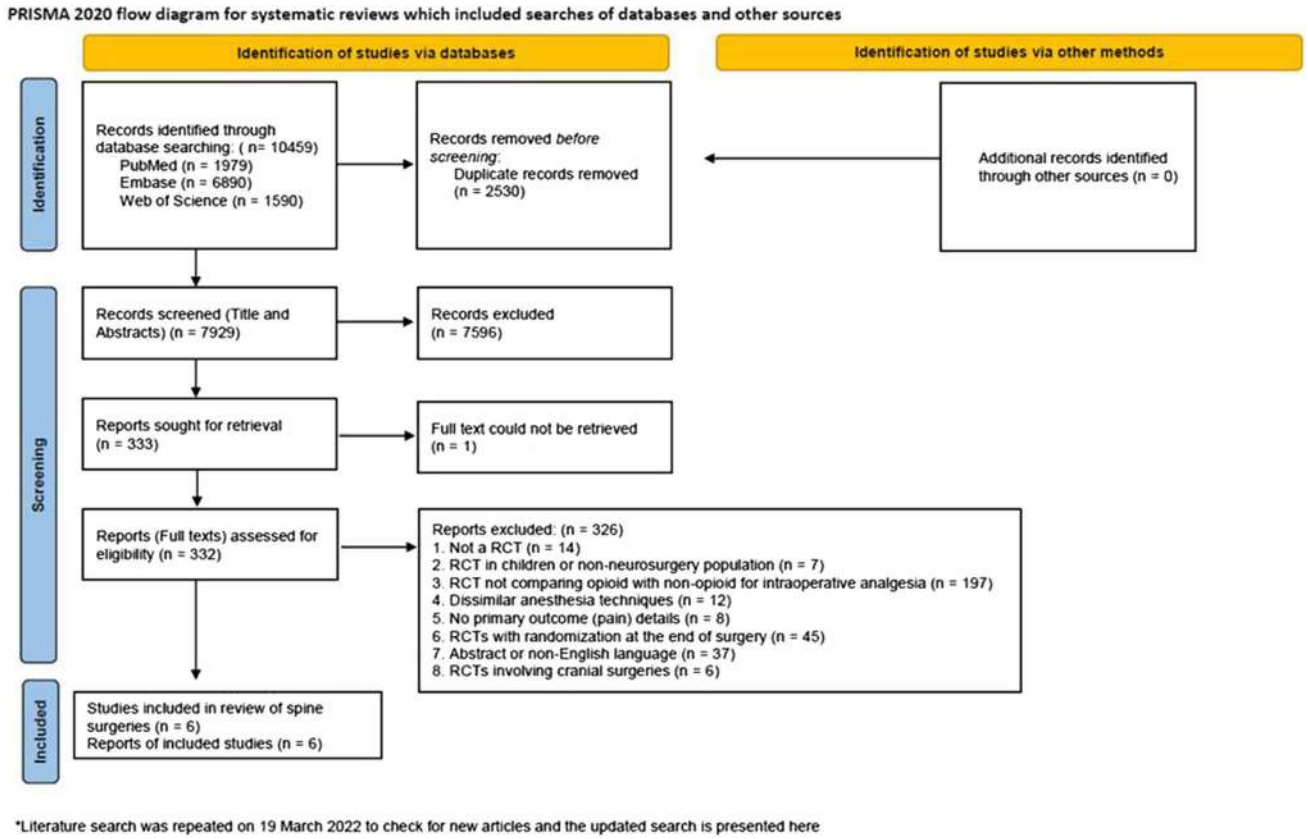

Fig. 1 PRISMA flow diagram informing records obtained after search of databases

one adverse event and four studies at least one recovery characteristic.

The time points of postoperative pain assessment varied from immediately after surgery up to 48 h with most studies reporting pain scores at 1 and 24 h after surgery. Hence, meta-analysis was performed for pain scores at these two time points. All the studies reported pain scores as visual analog scale except one where pain score was not informed. One study reported pain on a 0 to 100 scale [11], which we converted to 0–10 scale for pooling. The time for first analgesic requirement and 24-h opioid consumption after surgery were reported by three studies each.

There was no difference in pain score between opioid ($n=101$) and non-opioid ($n=101$) group at 1 h after surgery: 4 studies, mean difference (MD) = 0.65 units, 95% confidence intervals (CI) [−0.12 to 1.41], $p=0.10$. (Figure 3a) However, a statistically significant but clinically nonsignificant reduction in pain score was observed with non-opioid ($n=71$) compared to opioid ($n=71$) analgesia at 24 h after surgery: 3 studies, MD = 0.75 units, 95%CI [0.03 to 1.46], $p=0.04$. (Figure 3b) The time for first postoperative analgesic requirement was longer in the non-opioid group (MD = 45.06 min, 95%CI [17.62 to 72.50], $p=0.001$) (Figure 3c), and morphine consumption during first 24 h after surgery was higher in the opioid group (MD = 4.54 mg, 95% CI [3.26 to 5.82], $p<0.00001$). (Figure 3d) In one study [13], hydromorphone was used and this was converted to morphine equivalent using a conversion of 1 mg hydromorphone equals to 5 mg of morphine [22].

The adverse events evaluated in the included studies were PONV ($n=5$), shivering ($n=3$) and perioperative bradycardia ($n=2$). The incidence of PONV was significantly higher in the opioid group as compared to non-opioid group (RR = 2.15, 95% CI [1.37 to 3.38], $I^2=1\%$, p = 0.0009). (Figure 4a) The incidence of postoperative shivering was also significantly higher in the opioid group vis-à-vis non-opioid group (RR = 2.52, 95% CI [1.08 to 5.89], $I^2=15\%$, $p=0.03$). (Figure 4b) The incidence of perioperative bradycardia was, however, significantly lower with opioid analgesia as compared to non-opioid analgesia (RR = 0.35, 95%CI [0.17 to 0.71], $I^2=0\%$, $p=0.004$). (Figure 4c) We did not perform a meta-analysis for sedation as the sedation scores used were different in all the studies reporting it (Ramsay Sedation Scale[15], four-point scale[11] and an unnamed scale[14])

Table 1 Characteristics of included studies: Population, intervention, comparator, outcome and study duration

Sl No	Study author, Year, Population	Surgery duration (min)		Age (years) Mean [SD]		Male gender (n/total)		Intervention	Comparator	Primary pain outcome assessed	Follow-up period
		Opioid	Non-opioid	Opioid	Non-opioid	Opioid	Non-opioid	Opioid [Route]	Non-opioid [Route]		
1	Alansary 2019 lumbar disk surgery	103.9 [5.7]	102.6 [5.9]	41.5 [7.4]	43.2 [7.4]	23/40	27/40	Fentanyl [Epidural]	Dexmedetomidine [Epidural]	Time to first analgesic requirement	24 h
2	Aveline 2006 lumbar disk surgery	36.8 [14.8]	40.6 [18.1]	44.4 [11.2]	44.8 [8.4]	10/23	11/22	Morphine [IV]	Ketamine [IV]	24-h morphine consumption	48 h
3	Hwang 2015 posterior lumbar interbody fusion	171.1 [23.2]	177.2 [23.9]	65.1 [5.3]	65.9 [5.8]	8/18	8/19	Remifentanil [IV]	Dexmedetomidine [IV]	Postoperative pain score	48 h
4	Janatmakan 2021 Lumbar discectomy	Not clear	Not clear	45.2 [6.72]	46.7 [6.83]	17/30	16/30	Remifentanil [IV]	Dexmedetomidine [IV]	Postoperative pain score	24 h
5	Rahimzadeh 2015 Posterior spinal fusion	Not clear	Not clear	54 [7.7]	55.6 [9.0]	21/30	18/30	Remifentanil [IV]	Dexmedetomidine [IV]	Postoperative pain score	6 h
6	Turgut 2008 lumbar laminectomy	85	84	42.6 [9.0]	36.5 [10.3]	9/25	8/25	Fentanyl [IV]	Dexmedetomidine [IV]	Time to first analgesic requirement	Not clear

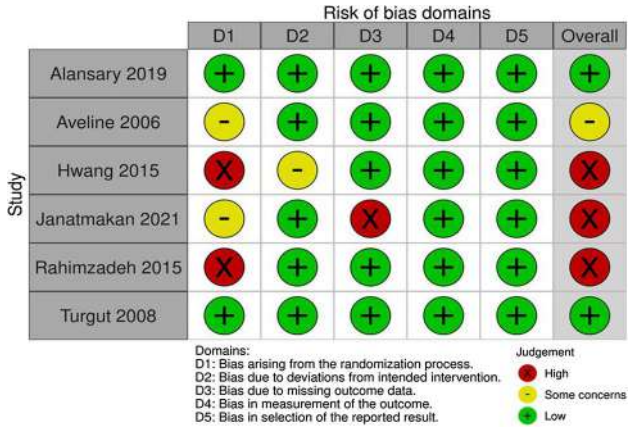

Fig. 2 Potential RoB of included studies for various domains

and at different time points (at extubation, in the PACU and overall during the 48-h study period). No study reported respiratory depression while only one study reported pruritis (15% versus 0% in opioid and non-opioid group)[15].

The recovery characteristics between opioid and non-opioid groups were reported in the included studies as time to respond to verbal commands ($n=2$), PACU discharge time ($n=3$), and peri-extubation HR ($n=2$) and MBP ($n=2$). The time to respond to verbal commands was significantly shorter with opioid analgesia than with non-opioid analgesia (MD = −14.25 min, 95% CI [−20.86 to −7.64], $I^2=82\%$, $p<0.0001$). (Figure 5a) The peri-extubation HR was significantly higher in opioid group than non-opioid group (MD = 12.81 beats per minutes, 95% CI [8.06 to 17.55], $I^2=74\%$, $p<0.0001$). (Figure 5b) The peri-extubation MBP was also higher in opioid group as compared to non-opioid group (MD = 10.99 mmHg, 95% CI [1.55 to 20.43], $I^2=93\%$, $p=0.02$). (Figure 5c) The discharge time from the PACU was similar for patients receiving opioid and non-opioid analgesia during surgery (MD = −4.88 min, 95% CI [−16.86 to 7.10], $I^2=97\%$, $p=0.42$) (Figure 5d).

Our planned subgroup analysis for individual opioid and non-opioid drugs was not possible due to an insufficient number of studies for analysis of our primary outcome. The GRADE quality of evidence was assessed using GRADEpro GDT software [23] and is presented in Table 2. The certainty of evidence on GRADE assessment was low to very low for pain score at 1 and 24 h after surgery, moderate to low for adverse events (PONV and shivering) and low to very low for recovery outcomes (awakening time and PACU discharge). Most were rated low due to RoB and inconsistency, imprecision or indirectness for outcome measures.

Publication bias

Publication bias was checked for primary outcome using funnel plots and Egger's test. We did not find publication bias, as evidenced by symmetric funnel plot [Appendix S3A and B: Funnel plot for postoperative pain scores at 1 and 24 h, respectively] and statistically insignificant Egger's test ($P=0.092$ and 0.088 for 1 and 24 h pain scores).

Discussion

Summary of findings

In this systematic review and meta-analysis of patients undergoing spine surgery, postoperative pain scores were similar at 1 h but lower at 24 h after surgery with intraoperative use of non-opioid as compared to opioid analgesia. Also, the time for the first analgesic requirement was longer and morphine consumption during the first 24 h after spine surgery was lesser in the non-opioid analgesia group vis-à-vis opioid group. Opioid-related adverse effects of PONV and shivering were higher and perioperative bradycardia was lower with opioid analgesia. Although the response time to verbal commands was faster with opioids, the PACU discharge time was similar between opioid and non-opioid groups. However, peri-extubation HR and MBP were lower with non-opioid analgesia as compared to opioid analgesia group.

Review of literature

More than 50% of patients report pain during the first 24 h after spine surgery [24]. This high incidence of pain is despite opioids being the most common analgesics used during the intraoperative period. Moreover, opioid adverse effects are common. To overcome these limitations, opioid alternatives are studied. However, very few RCTs have directly compared intraoperative opioids with non-opioid analgesics with regard to postoperative pain in patients undergoing spine surgery [11–16]. Most of the included studies reported using remifentanil and dexmedetomidine as the opioid and non-opioid analgesic drugs, respectively, during the intraoperative period. Remifentanil is an ultra-short acting analgesic while dexmedetomidine has a significant residual analgesic effect after discontinuation of the infusion [13, 25]. The difference in postoperative pain scores in this review between opioid and non-opioid groups at 24 h but not at 1 h after spine surgery could reflect these differential drug effects or remifentanil-associated hyperalgesia [26]. The overall pain scores in the non-opioid group were 0.65 units and 0.75 units lower than the opioid group at 1 h

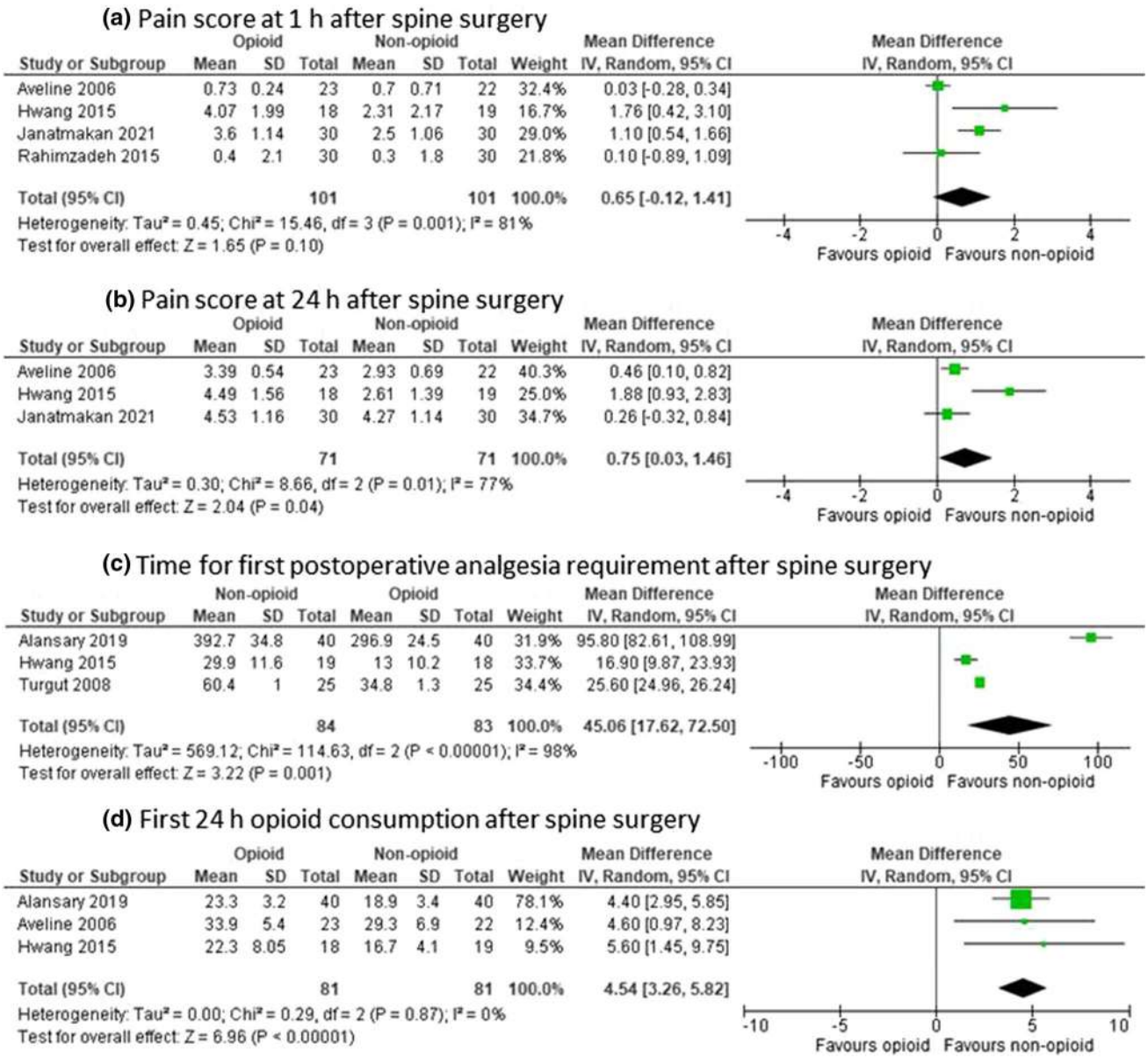

Fig. 3 **a** Postoperative pain score at 1 h after surgery. **b** Postoperative pain score at 24 h after surgery. **c** Time for first postoperative analgesia requirement. **d** First 24 h opioid consumption after surgery

and 24 h, respectively. A previous systematic review noted that the minimum clinically important difference ranged between 0.8 and 4 cm on a 0–10 cm scale for acute pain [27]. Considering this finding, our observation of smaller difference in pain scores can be considered as not important [28]. However, we observed meaningful differences in the time to first rescue analgesia and morphine requirements in the first 24 h after surgery. In addition, we observed reduced risks of adverse events (PONV and shivering) in the non-opioid group. These findings of better pain-related effects and lower drug-related adverse events with non-opioids are likely to influence anesthesiologist's clinical decisions regarding choice of intraoperative analgesics for postoperative pain management.

Fear of opioid side effects has often led to under treatment of pain. However, several non-opioid analgesia options are available and effective for pain relief in patients undergoing spine surgery. Non-opioid multimodal intraoperative analgesia including loco-regional technique such as erector spinae plane block [5, 8], and systemic drug infusions of dexmedetomidine [29], ketamine [30], lignocaine [31] and gabapentinoids [32], and drugs such as NSAIDs, cyclooxygenase-2 inhibitor and paracetamol [33] have shown to provide better analgesia and reduce opioid consumption

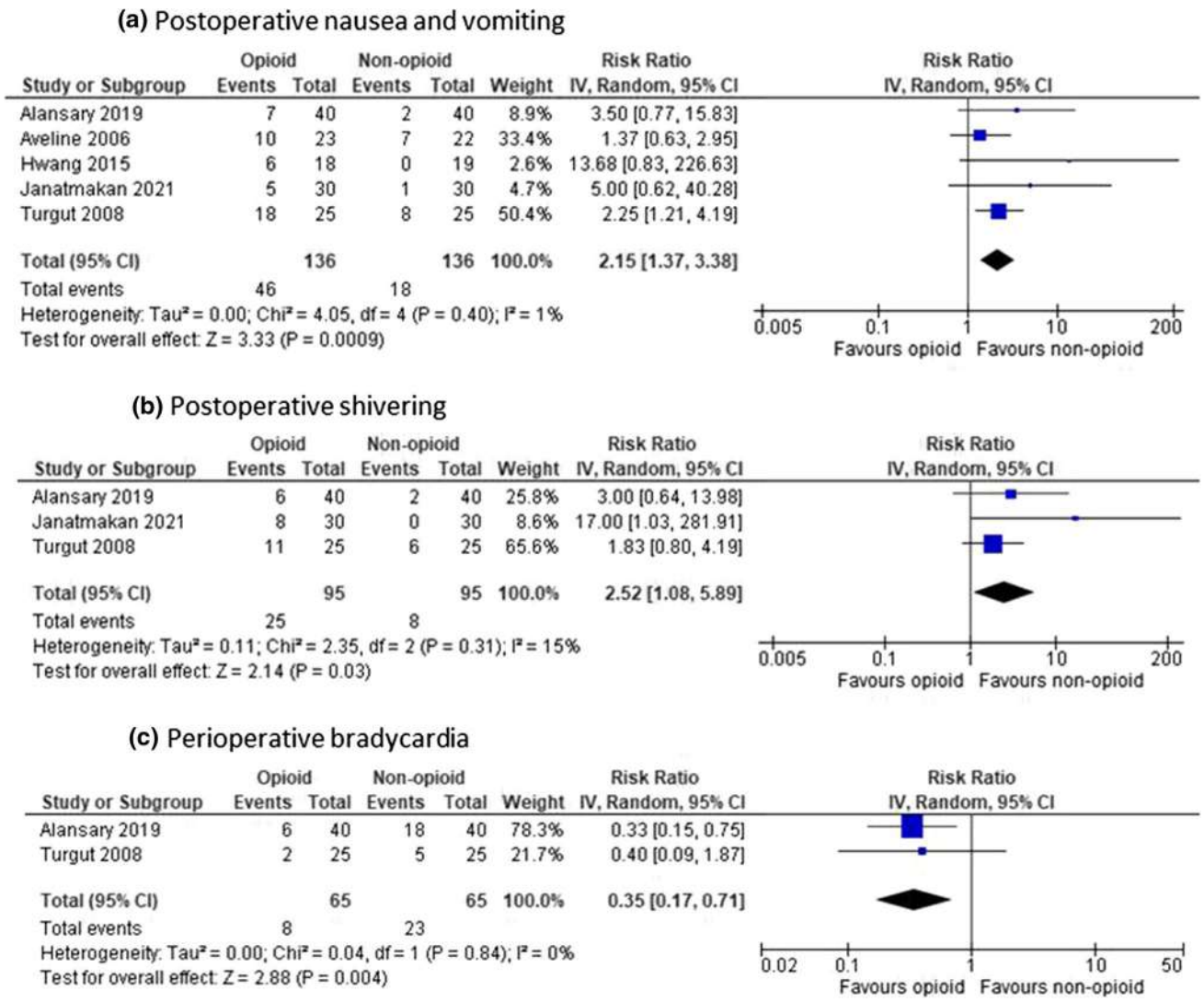

Fig. 4 **a** Comparison of postoperative nausea and vomiting. **b** Comparison of postoperative shivering. **c** Comparison of perioperative bradycardia

(consequently, reduce adverse effects) in patients undergoing spine surgery as compared to opioids alone [4]. Most of these non-opioid analgesics are used in combination and not as the sole analgesic. In our review too, most of the included studies reported using less potent non-opioid analgesics such as paracetamol or NSAIDs during or at the end of surgery in both opioid and non-opioid groups. Ideally, loco-regional and multimodal analgesia must be maximally employed for pain relief as non-opioid interventions and compared with opioids. Consequently, for such comparisons, the effect size is likely to be different.

Strengths and limitations

This is the only review to our knowledge that compared opioid and non-opioid intraoperative analgesia for postoperative pain in patients undergoing spine surgery. Previous reviews reported mainly on postoperative analgesia comparisons with regard to pain outcome. Our findings will help anesthesiologists make informed evidence-based decisions on the choice of intraoperative analgesia for spine surgery. However, our review has certain limitations. We observed a lack of uniformity in reporting pain outcomes such as time of assessments and type of opioid and non-opioid analgesics used in the included studies. Two studies reported using bolus fentanyl (opioid) in both the groups at anesthetic induction to ablate nociceptive response to laryngoscopy and intubation before randomization to study interventions. The residual effect of fentanyl at induction could influence postoperative pain, though this is unlikely as the duration of action of fentanyl is between 30 and 60 min [34]. We could not perform

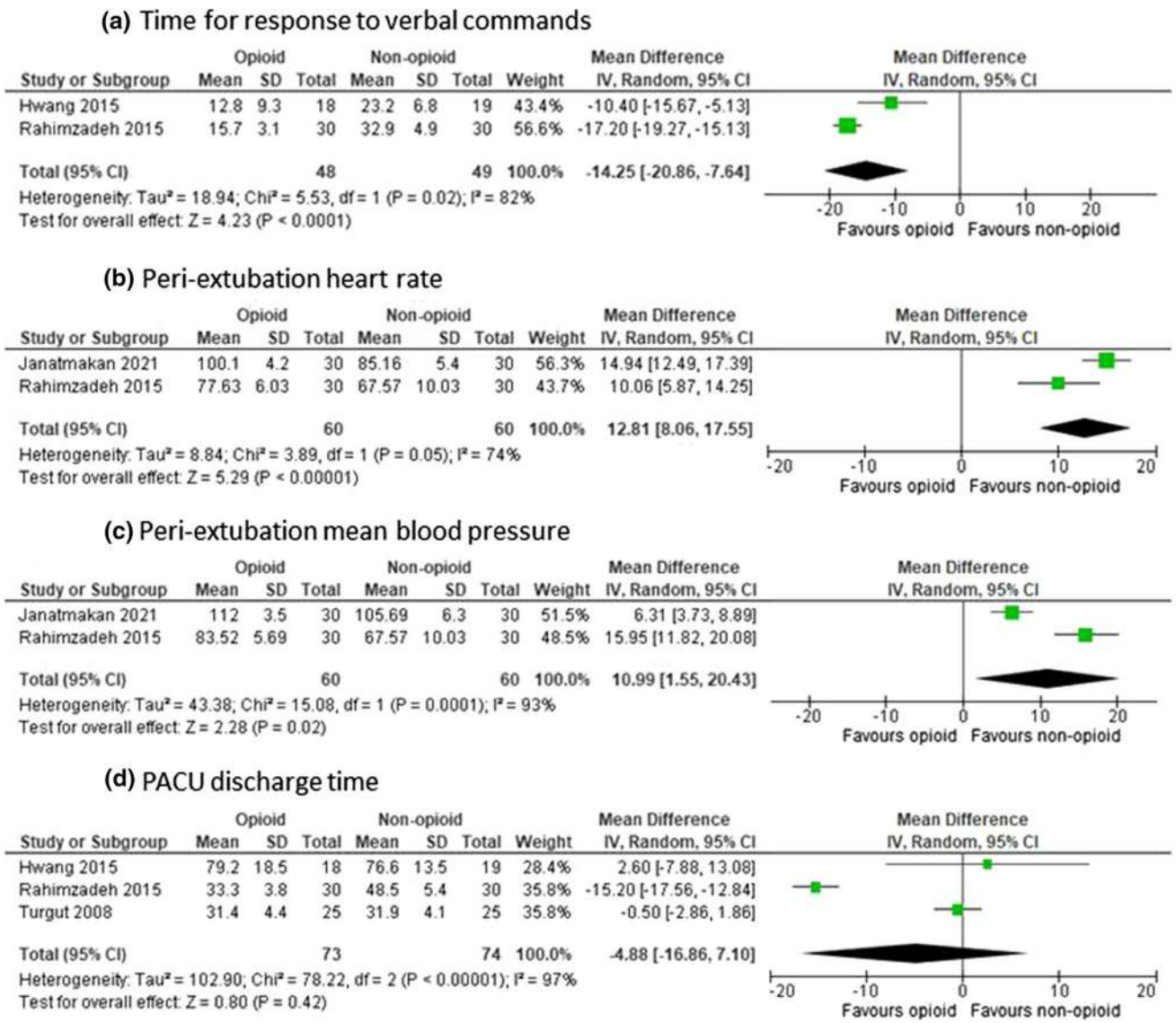

Fig. 5 **a** Time to respond to verbal commands. **b** Comparison of peri-extubation heart rate. **c** Comparison of peri-extubation mean blood pressure. **d** Comparison of discharge time from the post-anesthesia care unit

a meta-analysis for postoperative sedation as the scores used, time of assessment and method of reporting central tendency and variance were different in different studies. We also could not perform analysis for intraoperative hemodynamics as the time point of assessment after the initiation of study interventions could not be agreed upon. However, we performed a meta-analysis for important pain and adverse effects outcomes that matter to the clinicians and patients. Significant heterogeneity was observed for some of the outcomes studied which could have been due to the small sample size or few events in the RCTs. Lastly, this review is limited by the quality of included studies. The limitation emphasizes the need for more research with good quality RCTs having large samples and similar opioid and non-opioid interventions in order to find the best drug combination and dosing regimen.

Conclusions

Intraoperative use of non-opioid analgesia in patients undergoing spine surgery probably reduces postoperative pain at 24 h, delays time to rescue analgesia and reduces opioid consumption in the first 24 h after surgery with fewer adverse events of PONV and shivering. However, the high RoB and heterogeneity resulted in low to very low certainty of

Table 2 GRADE certainty of evidence for study outcomes

Opioid compared to non-opioid for perioperative pain management in spine neurosurgery

Patient or population: perioperative pain management in spine neurosurgery
Setting: perioperative period
Intervention: opioid
Comparison: non-opioid

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with non-opioid	Risk difference with opioid
Pain score at 1 h after surgery assessed with: VAS Scale from: 0 to 10 follow-up: mean 1 hour	202 (4 RCTs)	⨁◯◯◯ Very low[a,b,c]	-		MD **0.65 higher** (0.12 lower to 1.41 higher)
Pain score at 24 h after surgery assessed with: VAS Scale from: 0 to 10 follow-up: mean 24 hours	142 (3 RCTs)	⨁⨁◯◯ Low[a,b]	-		MD **0.75 higher** (0.03 higher to 1.46 higher)
Adverse event: Postoperative Nausea Vomiting (PONV) assessed with: presence or absence	272 (5 RCTs)	⨁⨁◯◯ Low[a,d]	**RR 2.15** (1.37 to 3.38)	132 per 1,000	**152 more per 1,000** (49 more to 315 more)
Adverse event: Shivering assessed with: presence or absence	190 (3 RCTs)	⨁⨁⨁◯ Moderate[a]	**RR 2.52** (1.08 to 5.89)	84 per 1,000	**128 more per 1,000** (7 more to 412 more)
Time to respond to verbal commands (Awakening time) assessed with: observed minutes	97 (2 RCTs)	⨁⨁◯◯ Low[b,e]	-		MD **14.25 lower** (20.86 lower to 7.64 lower)
PACU discharge time assessed with: observed minutes	147 (3 RCTs)	⨁◯◯◯ Very low[a,b,c]	-		MD **4.88 lower** (16.86 lower to 7.1 higher)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Risk of Bias arising from randomization process, missing outcome data, measurement of outcome and selection of reported result
b. Inconsistency- variation in effect, heterogeneity
c. Imprecision - confidence interval crosses the clinical decision threshold
d. Indirectness- nausea and/or vomiting reported
e. Indirectness - Outcomes tested included time to eye opening or obeying commands

evidence on GRADE assessment for the outcomes studied. Considering the minimal difference in postoperative pain scores, the available evidence does not support intraoperative use of non-opioid over opioid analgesia in patients undergoing spine surgery. More research with good quality primary studies is needed before change in analgesia practice is contemplated.

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Declarations

Conflict of interest Authors have nothing to declare with regards to competing interests.

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CHAPTER 9

DISCUSSION

Assessment and management of perioperative pain in neurosurgical patients

The research questions I outlined generated new insights into the assessment and management of pain in neurosurgery population. We found that assessment and management of postoperative pain was not uniform throughout the world. We conducted a national survey among Indian neuroanesthesiologists with the objective of capturing hospital and pain characteristics that predicted implementation of structured pain assessment protocol and use of opioids for postoperative pain management (chapter 2). The response rate was 55% among the 524 anesthesiologists to whom the questionnaire was sent. The survey revealed that structured protocol for assessment of pain was present in only 41% of the healthcare establishments. Also, the use of opioids for management of postoperative pain was very low at 15% when compared to the developed countries, with most Indian hospitals employing non-opioid drugs to treat pain after neurosurgical procedures. Use of structured protocol for postoperative pain assessment was more likely in private hospital setup, in establishments that used a validated pain scale, and when pain was reported to be of higher intensity. Postoperative opioid use was predicted by the availability of structured pain protocol. [1] The probable reasons for reduced opioid use for postoperative pain management in India could be fear of opioid side-effects, increased use of non-opioids and loco-regional analgesia, and increased pain tolerance due to genetic and ethnic factors.

Postoperative pain is common but an undesirable complication after neurosurgery. While data about its incidence and predictors are available for the developed countries, such information is lacking for Indian population. In our

prospective observational study of patients undergoing craniotomy, we aimed to assess the incidence, risk factors, and impact of acute postoperative pain after intracranial neurosurgeries (chapter 3). A total of 497 patients were recruited and pain was assessed using a numerical rating scale (NRS) score. Moderate-to-severe postoperative pain (NRS 4 to 10) at any time-point during the first three postoperative days was reported by 65.5% of patients, with the highest incidence reported on day 1 after surgery (50%) and least on day 3 (24%). Presence of preoperative pain and pain immediately after surgery predicted the occurrence of significant pain up to three days. Postoperative pain severely affected the quality of sleep on the first two nights after surgery. However, in contrast to earlier studies, the overall patient satisfaction was noted to be higher in patients having significant pain (submitted data). The probable reasons for this unusual finding could be that patient satisfaction assessment in this study was reported by patients for overall perioperative care (which were met, hence higher satisfaction) and not exclusively about pain. It is also possible that patients reported higher satisfaction despite significant pain when they felt prompt effort was made to treat pain and provide relief.

Surgery is the primary cause for postoperative pain. However, there may be other noxious stimuli in the intraoperative period that can produce nociception. Laryngoscopy and tracheal intubation is an essential procedure for providing general anesthesia in patients undergoing neurosurgery. Intubation results is a noxious stimulation that induces a significant stress response. The extent of hemodynamic activation is considered to represent the level of nociception.

Analgesia nociception index (ANI) is an objective parameter that provides information about parasympathetic (low nociceptive stress) and sympathetic (high nociceptive stress) balance and reflects the degree of intraoperative nociception/analgesia and has been evaluated in neurosurgical patients. [2, 3] We studied the changes in ANI and hemodynamics during anesthetic induction and intubation, and their correlation during tracheal intubation in sixty patients undergoing elective brain tumor surgeries (chapter 4). Anesthetic induction was associated with reduction in ANI and blood pressure (BP), and increase in heart rate (HR). Tracheal intubation resulted in an increase in HR and MBP, with a decrease in ANI below the threshold of 50 (a linear negative correlation). [4] What this means is that ANI can be incorporated into clinical practice as a monitoring modality to objectively assess the magnitude of pain and the adequacy of analgesia during anesthesia.

Stress response to a surgical stimulus is mediated by the sympathetic autonomic nervous system and manifests as increases in the hemodynamic and neuroendocrine parameters. Another method of assessing surgical stress in an objective and continuous manner is using a parameter called surgical pleth index (SPI) that is displayed in the multi-parameter patient monitor. The SPI ranges from 0 to 100, with 100 representing maximum stress level and 0 corresponding to absence of surgical stress. The SPI is derived from normalized heartbeat interval (HBInorm) and plethysmographic pulse-wave amplitude (PPWAnorm) and is calcuated as follows: SSI = 100–(0.7*PPWAnorm + 0.3*HBInorm). [5] Studies have demonstrated SPI to be a better measure of nociception/antinociception balance than entropy and

HR. [6] Thus, SPI can also be used to titrate intraoperative analgesic administration. Opioids are the most commonly used analgesics to minimize the stress associated with surgery. However, use of opioids is associated with side effects and therefore, there is a gradual shift in the perioperative pain management towards non-opioid analgesia. Dexmedetomidine is an alpha-2 agonist used in the intraoperative period to minimize opioid and anesthesia requirements during neurosurgeries. [7] However, the effect of opioid and non-opioid analgesia in ablating stress response during surgery using SPI and blood biomarkers is not evaluated. We compared the changes in SPI and few biomarkers of surgical stress between opioid (fentanyl, 1 µg/kg/h) and non-opioid (dexmedetomidine, 0.5 µ/kg/h) analgesia during craniotomies in 24 patients with brain tumors (chapter 5). We observed similar stress response to surgery with opioid and non-opioid intraoperative analgesia as assessed by SPI and blood markers such as cortisol, glucose, and pH. [8] The lessons learnt from this study are that both opioid and non-opioid analgesics are appropriate to ablate the nociceptive response arising from surgery, and that SPI can be a reliable non-invasive continuous monitor to quantify the surgical stress and determine the effect of analgesia during anesthesia and surgery.

Moderate to severe postoperative pain is reported by many patients despite the use of potent opioids during craniotomies. Moreover, opioid side effects are well known and adverse effects such as respiratory depression can be problematic after neurosurgery. [9] This has generated interest in exploring the use of opioid free analgesia regimens during anesthesia for craniotomies. [10] Non-opioid agents such as dexmedetomidine have been successfully used as primary analgesic during non-

neurological surgeries. We assessed the feasibility of conducting a large randomized controlled trial (RCT) comparing fentanyl with dexmedetomidine for perioperative analgesia during craniotomy (chapter 6). Twenty four patients were randomized equally to receive either fentanyl 1 μg/kg/h or dexmedetomidine 0.5 μg/g/h as primary intraoperative analgesic drug. We demonstrated feasibility by recruiting the desired number of patients and 100% adherence to protocol. There was no difference in the rescue fentanyl consumption (total μgs) between fentanyl and dexmedetomidine groups [median and interquartile range of 25 (0-50) and 0 (0-50) respectively; P = 0.844] and postoperative pain at 15 and 60 minutes. Also, adverse events occurred similarly in both the groups. [11] Our initial findings encourage the use of non-opioid analgesia with dexmedetomidine for intracranial neurosurgeries. The next step would be to conduct a large multicentre RCT to confirm our findings and enhance generalizability, and eventually establish non-opioid intraoperative analgesia as a standard clinical practice.

Since there are very few studies comparing opioid and non-opioid analgesia in patients undergoing intracranial surgeries, a systematic review and meta-analysis of these trials would be ideal to estimate the pooled evidence. In this regard, we synthesized evidence from RCTs comparing opioid and non-opioid intraoperative analgesia during craniotomies (chapter 7). A total of 10459 records were obtained by searching Medline, EMBASE and Web of Science databases and finally six eligible RCTs were included. There was no difference in pain scores between opioid and non-opioid analgesia at one and twenty-four hours after surgery: mean difference (MD) =1.11 units, 95% confidence intervals (CI) [-0.16 to 2.38], p=0.09, and MD =-0.06

units, 95%CI [-1.14 to 1.01], p=0.91, respectively. The time for first postoperative analgesic requirement was shorter with opioids but not statistically significant (MD =-84.77 minutes, 95%CI [-254.65 to 85.11], p=0.33). Postoperative nausea and vomiting was similar but shivering was more in opioid group than non-opioid group. The GRADE certainty of evidence was low for most outcomes that were studied. The evidence is low predominantly because of high risk of bias (RoB) in the primary RCTs, and inconsistency or imprecision in the pain outcomes measured in these studies. Thus, the current evidence does not suggest superiority of intraoperative non-opioid analgesia over opioid analgesia for postoperative pain management in patients undergoing craniotomy. [12] Additional good quality large multicentre trials are needed to overcome the limitations and bring certainty to this debate but may be difficult due to the many types of opioids and non-opioid analgesics used during craniotomies, different time-points of pain assessments needed, and challenges in arriving at the duration, route, dose and method (bolus or infusion) of administration.

Non-opioid techniques including recently introduced erector spinae plane block [13], and systemic drug infusions of dexmedetomidine [14], ketamine [15], and lignocaine [16] are increasingly used for perioperative analgesia in patients undergoing spine surgeries. Through another systematic review, we evaluated the pooled evidence regarding the effect of opioid and non-opioid intraoperative analgesia on acute postoperative pain and adverse events in spine surgery population (chapter 8). Six studies were eligible for inclusion for meta-analysis. The difference in postoperative pain scores between opioids and non-opioids was not

significant at 1 h but significantly favored non-opioids at 24 h after surgery. Other pain outcomes were also better in non-opioid group, with time for first postoperative analgesic requirement being shorter, and morphine consumption during first 24 h after surgery being higher with opioids. Adverse effects of postoperative nausea and vomiting and shivering were also lower with non-opioid analgesia. [17] However, high RoB in individual studies and inhomogeneity possibly from small sample size resulted in low-to-very low certainty of evidence on GRADE assessment for pain outcomes. Conducting additional RCTs in future to overcome these limitations is desirable, but will be challenging due to lack of uniformity in pain assessment time-points and use of several different types of opioid and non-opioid analgesics both during and after spine surgery.

Conclusions

Acute postoperative pain is a significant problem in patients undergoing cranial neurosurgery despite administration of standard perioperative analgesia. The use of structured pain assessment protocol and opioids for postoperative pain management is less common in neurosurgical patients in India. The changes in ANI during intubation correlate significantly with the changes in hemodynamic parameters. Both fentanyl and dexmedetomidine similarly ablate stress response to craniotomy as assessed by SPI and blood biomarkers. The need for rescue opioids and postoperative pain scores are similar with opioid and non-opioid analgesia used during craniotomy. This finding was confirmed in our systematic review of opioid and non-opioid analgesia used during craniotomies. However, for spine surgeries,

our systematic review showed intraoperative non-opioid analgesia to be superior to opioids. In summary, this PhD identified certain questions regarding pain assessment and management in neurosurgical population, and obtained some important answers which might benefit clinicians in the perioperative care of these patients.

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CHAPTER 10

SUMMARY

SUMMARY

Postoperative pain is common but undesirable after neurosurgery. Pain assessment is vital for effective treatment. Many developed nations assess pain using a structured format and manage pain predominantly using opioids. In our national survey among Indian neuroanesthesiologists (chapter 2), we noted that structured format for assessing pain was used by less than half of the healthcare facilities and opioid usage was minimal for postoperative pain management.

There is limited data regarding the burden of postoperative pain in neurosurgical patients in the Indian scenario. In our prospective observational study (chapter 3), we observed that every two out of three patients report moderate-to-severe pain at some point in the first three days after cranial neurosurgery. Presence of preoperative pain and pain in the post-anesthesia care unit predicted the occurrence of significant pain during the first three days after surgery.

Tracheal intubation, an essential part of general anesthesia for neurosurgical procedures, is a noxious stimulation that elicits acute stress response manifesting as increased heart rate and blood pressure. The Analgesia Nociception Index (ANI) is an objective parameter that quantifies the degree of nociception during noxious stimulation. We observed negative correlation between ANI and hemodynamic parameters during intubation (chapter 4).

Surgery results in trauma, tissue injury, and inflammation, which activate peripheral nociceptors to induce nociception. Stress response to surgery manifests as changes in hemodynamic and neuroendocrine parameters. The SPI is a monitoring parameter that measures surgical stress and nociception. Opioids are the

predominant analgesics used during neurosurgery to ablate stress response to surgery. In our study (chapter 5), we observed similar stress response during surgery for brain tumors with opioid (fentanyl) and non-opioid (dexmedetomidine) analgesia as assessed by SPI and blood markers such as cortisol, glucose, and pH.

Non-opioid analgesia is explored as an alternative to opioids to overcome their adverse effects. In our pilot RCT, we established feasibility of conducting a large-scale RCT comparing intraoperative dexmedetomidine versus fentanyl for postoperative pain outcomes and found dexmedetomidine to be non-inferior to fentanyl for perioperative analgesia during craniotomies (chapter 6).

In our systematic review and meta-analysis of trials comparing intraoperative opioids with non-opioids for craniotomies (chapter 7), we found that both analgesia techniques were similar with regards to postoperative pain parameters.

Non-opioid intraoperative analgesia however was found to be superior to opioid analgesia for pain outcomes and adverse effects in patients undergoing spine surgeries based on the available evidence in our systematic review (chapter 8).

Considering the ability of newer continuous monitors to detect intraoperative nociception/pain, it is prudent to include them in routine clinical practice. The high incidence of postoperative pain despite using opioids during surgery and recent evidence on the effectiveness of non-opioid analgesia necessitates the implementation of multi-modal analgesia techniques for postoperative pain management in neurosurgical patients. Large well-conducted RCTs are needed to confirm the benefits of non-opioid analgesia over opioids as shown in smaller clinical trials.

SAMENVATTING

Postoperatieve pijn is veel voorkomend maar ongewenst na neurochirurgie. Pijnbeoordeling is van vitaal belang voor een effectieve behandeling. Veel ontwikkelde landen beoordelen pijn met behulp van een gestructureerd formaat en behandelen pijn voornamelijk met behulp van opioïden. In ons nationale onderzoek onder Indiase neuroanesthesiologen (hoofdstuk 2) merkten we op dat een gestructureerd formaat voor het beoordelen van pijn door minder dan de helft van de zorginstellingen werd gebruikt en dat het gebruik van opioïden minimaal was voor postoperatieve pijnbestrijding.

Er zijn beperkte gegevens over de belasting van postoperatieve pijn bij neurochirurgische patiënten in het Indiase scenario. In onze prospectieve observationele studie (hoofdstuk 3) hebben we vastgesteld dat elke twee op de drie patiënten matige tot ernstige pijn meldt op enig moment in de eerste drie dagen na craniale neurochirurgie. Aanwezigheid van preoperatieve pijn en pijn in de postanesthesieafdeling voorspelden het optreden van significante pijn gedurende de eerste drie dagen na de operatie.

Tracheale intubatie, een essentieel onderdeel van algemene anesthesie voor neurochirurgische procedures, is een schadelijke stimulatie die een acute stressreactie opwekt die zich manifesteert als een toename van de hartslag en bloeddruk. De Analgesie Nociceptie-index (ANI) is een objectieve parameter die de mate van nociceptie tijdens schadelijke stimulatie kwantificeert. We observeerden een negatieve correlatie tussen ANI en hemodynamische parameters tijdens intubatie (hoofdstuk 4).

Chirurgie resulteert in trauma, weefselbeschadiging en ontsteking, die perifere nociceptoren activeren om nociceptie te induceren. Stressrespons op chirurgie manifesteert zich als veranderingen in hemodynamische en neuro-endocriene parameters. De SPI is een monitoringparameter die chirurgische stress en nociceptie meet. Opioïden zijn de overheersende analgetica die tijdens neurochirurgie worden gebruikt om de stressreactie op een operatie weg te nemen. In onze studie (hoofdstuk 5) hebben we een vergelijkbare stressrespons waargenomen tijdens operaties voor hersentumoren met opioïde (fentanyl) en niet-opioïde (dexmedetomidine) analgesie zoals beoordeeld door SPI en bloedmarkers zoals cortisol, glucose en pH.

Niet-opioïde analgesie wordt onderzocht als alternatief voor opioïden om hun nadelige effecten te overwinnen. In onze pilot-RCT hebben we de haalbaarheid vastgesteld van het uitvoeren van een grootschalige RCT waarin intraoperatieve dexmedetomidine werd vergeleken met fentanyl voor postoperatieve pijnuitkomsten en we vonden dat dexmedetomidine niet-inferieur was aan fentanyl voor perioperatieve analgesie tijdens craniotomieën (hoofdstuk 6).

In onze systematische review en meta-analyse van onderzoeken waarin intraoperatieve opioïden werden vergeleken met niet-opioïden voor craniotomieën (hoofdstuk 7), merkten we op dat beide analgesietechnieken vergelijkbaar waren met betrekking tot postoperatieve pijnparameters.

Niet-opioïde intra-operatieve analgesie bleek echter superieur te zijn aan opioïde analgesie voor pijnuitkomsten en bijwerkingen bij patiënten die een

wervelkolomoperatie ondergingen, gebaseerd op het beschikbare bewijs in onze systematische review (hoofdstuk 8).

Gezien het vermogen van nieuwere continue monitoren om intraoperatieve nociceptie/pijn te detecteren, is het verstandig om ze op te nemen in de dagelijkse klinische praktijk. De hoge incidentie van postoperatieve pijn ondanks het gebruik van opioïden tijdens chirurgie en recent bewijs over de effectiviteit van niet-opioïde analgesie maakt de implementatie van multimodale analgesietechnieken noodzakelijk voor postoperatieve pijnbeheersing bij neurochirurgische patiënten. Er zijn grote, goed uitgevoerde RCT's nodig om de voordelen te bevestigen van niet-opioïde analgesie ten opzichte van opioïden die in kleinere klinische onderzoeken worden gezien.

CHAPTER 11

VALORIZATION

Postoperative pain is a common yet distressing problem faced by patients and clinicians alike. No individual likes to suffer from pain and least so, patients undergoing neurosurgical procedures. Clinicians also are unhappy when their patients report pain after an otherwise successful surgery. Yet, despite several advances in technology and pharmacological products over the last several years to manage pain both during and after surgery, pain is one of the most commonly reported postoperative complications in neurosurgical patients. The five essential questions for pain treatment need to be carefully considered: which patient should when receive which drug in which dose and via which route. Therefore, there is a need to reflect on how to overcome this problem.

The assessment of pain is crucial for understanding the burden of this problem and to address it. Pain assessment and management in surgical patients vary considerably across the globe. We learned from our survey among Indian anesthesiologists that use of structured protocol for pain assessment is lacking and very few use opioids for pain management in the postoperative period after neurosurgery. This knowledge can be used to overcome the current gap and provide better healthcare to our patients. Implementation of pain protocols must be encouraged and facilitated. Subsequent analyses must address the limiting factors of successful implementation.

From our research, we understand that postoperative pain after brain surgery continues to remain a significant problem with every two in three patients reporting moderate-to-severe pain at some point during the initial three days after surgery. From this, we know that the current analgesia methods adopted are insufficient to

adequately manage pain and more efforts are needed in this direction. New clinical trials must be designed to identify the most effective analgesia technique with least side-effects.

Objective tools of intraoperative nociception assessment such as surgical pleth index and analgesia nociception index are not routinely employed in the intraoperative period. Today, these methods of nociception assessment are available for use in patients undergoing surgery under general anesthesia. These monitors help in the assessment of nociception levels and also in titrating the administration of analgesia. Postoperative pain is likely to be minimized by utilizing these parameters to guide intraoperative analgesia. Implementation can be facilitated by incorporating these parameters in the existing multi-parameter intraoperative patient monitors.

Opioids such as fentanyl, remifentanil, and morphine are the primary systemic analgesics used during the intraoperative period. However, due to their potential side effects, non-opioid analgesia options alone or in combination with opioids are increasingly adopted in anesthesia practice. From our preliminary research in patients undergoing brain surgeries, we observed that non-opioid analgesics are not inferior to opioids when used as sole analgesia technique with regards to pain outcomes or side effects. We also observed similar findings in our systematic review and meta-analysis of six trials involving craniotomy population. Our research provides confidence to adopt non-opioid analgesia techniques in our clinical practice especially when opioid analgesia presents an increased risk. The

dissemination of this finding will be facilitated by presentations at conferences and through scientific publications.

The available evidence as per our systematic review favors intraoperative non-opioid analgesia over opioids in patients undergoing spine surgeries with regards to pain outcomes and patient reported adverse effects. This knowledge will help healthcare providers to include and maybe eventually substitute non-opioid multimodal analgesia techniques in place of opioids as part of perioperative practice.

Overall, the knowledge gained from this research is likely to benefit clinicians in making informed choices based on the evidence regarding assessment and management of perioperative pain in order to improve overall health outcomes in neurosurgical patients. Towards this end, the five essential questions for pain treatment need to be carefully considered: *which patient* should *when receive which drug* in *which dose* and via *which route*.

CHAPTER 12

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Australia, Crawley, WA, Australia. He guided me in selection of the topic of my PhD thesis, helped me with the paper work, advised me on several aspects of meta-analysis and in short, was instrumental in the entire process of my PhD. He always responded promptly and guided me at every step whenever I contacted him, despite the time difference and his busy schedule. I could not have found a better mentor than him. Without his unflinching support and continuous supervision, this PhD would not have materialized. I convey my sincere thanks and regards to him.

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ABOUT THE AUTHOR

Dr Sriganesh Kamath was born on 22 July 1977 at Mulki, Karnataka, in India. He completed his Pre-University Board examinations (Science) in 1995 by securing 9th rank in the entire Karnataka state. He secured MBBS admission at the Karnataka Medical College, Hubli and completed internship in 2001. He completed MD Anesthesiology at Jawaharlal Nehru Medical College, Belgaum in 2005 securing 9th Rank in the Rajiv Gandhi University of Health Sciences MD Anaesthesia exit examination. The same year, he received DNB (Anaesthesiology) from National Board of Examinations, New Delhi. He completed DM (Neuroanesthesia) at Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum in 2008.

Dr Sriganesh joined the Department of Neuroanaesthesia at the National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru in March 2009 as an Assistant Professor (Adhoc). In June 2011, he was appointed as Assistant Professor on a permanent post. Subsequently, he was promoted as Associate Professor in 2012, Additional Professor in 2015 and Professor in 2019. In April 2022, he was appointed as Head of the Department, which he continues to hold till date.

In late 2015, Dr Sriganesh was awarded the Indian Council of Medical Research (ICMR) International Fellowship for Young Scientists. Using this, he completed Research Fellowship in Anesthesia/Pain from McMaster University, Hamilton, Canada. During his tenure at McMaster University, he learnt basics of conducting a systematic review, got trained in Evidence Based Clinical Practice and Health Research Methods, was part of research projects on pain and published a few collaborative papers with the McMaster research team.

In the last 18+ year post MD career, Dr Sriganesh has published 162 scientific papers in peer-reviewed biomedical journals in Neuroanesthesia, Neurocritical Care and Pain and 11 book chapters.

In the last 10 years, he has focussed on pain as his area of interest. He underwent short-term training in pain management in 2012 from Daradia Pain Hospital, Kolkata. He has been a life member of Indian Society for the Study of Pain (ISSP) since 2013 and regular member of the International Society for the Study of Pain since 2018. He served as an executive committee member of ISSP, Karnataka state from 2015-18. He started the NIMHANS Pain Clinic OPD and interventional pain procedure services in 2017. He has conducted several studies in perioperative pain and published them in reputed journals.

In recognition of his academic and research contributions, Dr Sriganesh received several awards such as Indian Society of Anaesthesiologists (ISA) Young Anaesthesiologist Award (2013), ISA Proficiency Award (2018, 2019, 2021), ISA President's Appreciation Award (2021) and ISA Bhopal Award for Academic Excellence (2022). Dr Sriganesh recently received a multi-centre grant from Department of Health Research, ICMR for comparing Non-opioid and Opioid Perioperative Analgesia In Neurosurgeries (NOPAIN Trial) and another grant from Cognitive Science Research Initiative of the Department of Science and Technology for a project titled "Effect of Intraoperative Dexmedetomidine on Postoperative Delirium and Cognitive Dysfunction after Brain Surgery: A Randomized Controlled Trial". He is the Lead for Specialty Centre for Clinical Trials (Neurology) of ICMR.

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PREPOSITIONS

1. Less than half of Indian anesthesiologists use structured protocol for pain assessment and very few use opioids for postoperative pain management after neurosurgery. (this thesis)
2. Every two in three patients report pain at some time point during the initial three days after neurosurgery for brain pathologies. (this thesis)
3. Analgesia nociception index, an objective monitor of parasympathetic (low nociceptive stress) and sympathetic (high nociceptive stress) balance, has a negative linear correlation with systemic hemodynamics during noxious stimuli of laryngoscopy and tracheal intubation. (this thesis)
4. In a pilot study, dexmedetomidine (non-opioid) appears to be non-inferior to fentanyl (opioid) for perioperative analgesia during craniotomies. Stress response to surgery as assessed by surgical pleth index and blood markers is similar with two techniques of intraoperative analgesia. (this thesis)
5. Intraoperative use of opioids and non-opioid analgesics result in similar postoperative pain relief in patients undergoing craniotomies. (this thesis)
6. Postoperative pain outcomes were better with intraoperative non-opioid usage compared to opioids in spine surgeries. (this thesis)
7. Pain is inevitable, suffering is optional
8. असतो मा सद्गमय। तमसो मा ज्योतिर्गमय। मृत्योर्मामृतं गमय ॥ ॐ शान्ति शान्ति शान्तिः ॥
   [From ignorance, lead me to truth; From darkness, lead me to light; From death, lead me to immortality. Om peace, peace, peace] – Sanskrit Prayer

9. सर्वे भवन्तु सुखिनः । सर्वे सन्तु निरामयाः । सर्वे भद्राणि पश्यन्तु । मा कश्चित् दुःख भाग्भवेत् ॥

   [May all be happy, May all be free from illness, May all see what is auspicious, May no one suffer] – Sanskrit Shloka

10. If you want to leave your footprints on the sands of time, do not drag your feet. - Dr A.P.J. Abdul Kalam, Wings of Fire

National Institute of Mental Health and Neuro Sciences (NIMHANS), Bengaluru