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Pain management after elective craniotomy

A systematic review with procedure-specific postoperative pain management (PROSPECT) recommendations

François P. Mestdagh, Patricia M. Lavand'homme, Géraldine Pirard, Girish P. Joshi, Axel R. Sauter and Marc Van de Velde, on behalf of the PROSPECT Working Group* of the European Society of Regional Anaesthesia and Pain Therapy (ESRA)

BACKGROUND Pain after craniotomy can be intense and its management is often suboptimal.

OBJECTIVES We aimed to evaluate the available literature and develop recommendations for optimal pain management after craniotomy.

DESIGN A systematic review using procedure-specific postoperative pain management (PROSPECT) methodology was undertaken.

DATA SOURCES Randomised controlled trials and systematic reviews published in English from 1 January 2010 to 30 June 2021 assessing pain after craniotomy using analgesic, anaesthetic or surgical interventions were identified from MEDLINE, Embase and Cochrane Databases.

ELIGIBILITY CRITERIA Each randomised controlled trial (RCT) and systematic review was critically evaluated and included only if met the PROSPECT requirements. Included studies were evaluated for clinically relevant differences in pain scores, use of nonopioid analgesics, such as paracetamol and NSAIDs, and current clinical relevance.

RESULTS Out of 126 eligible studies identified, 53 RCTs and seven systematic review or meta-analyses met the inclusion criteria. Pre-operative and intra-operative interventions that improved postoperative pain were paracetamol, NSAIDs, intravenous dexmedetomidine infusion, regional analgesia techniques, including incision-site infiltration, scalp nerve block and acupuncture. Limited evidence was found for flupirtine, intra-operative magnesium sulphate infusion, intra-operative lidocaine infusion, infiltration adjuvants (hyaluronidase, dexamethasone and α-adrenergic agonist added to local anaesthetic solution). No evidence was found for metamizole, postoperative subcutaneous sumatriptan, preoperative oral vitamin D, bilateral maxillary block or superficial cervical plexus block.

CONCLUSIONS The analgesic regimen for craniotomy should include paracetamol, NSAIDs, intravenous dexmedetomidine infusion and a regional analgesic technique (either incision-site infiltration or scalp nerve block), with opioids as rescue analgesics. Further RCTs are required to confirm the influence of the recommended analgesic regimen on postoperative pain relief.

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From the Department of Anaesthesiology, Cliniques Universitaires St Luc, University Catholic of Louvain, Brussels, Belgium (FPM, PML, GP), Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, Texas, USA (GPJ), Department of Anaesthesia and Intensive Care Medicine, Oslo University Hospital, Norway (ARS), Department of Anaesthesiology and Pain Therapy, Bern University Hospital – Inselspital, Bern, Switzerland (ARS), and Department of Cardiovascular Sciences, Section Anaesthesiology, KULeuven and UZLeuven, Leuven, Belgium (VdV)

Correspondence to François P. Mestdagh, Department of Anaesthesiology, University Catholic of Louvain, Cliniques Universitaires St Luc, 10 Avenue Hippocrate, Brussels 1200, Belgium.
E-mail: francois.mestdagh@uclouvain.be

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Recommendations for patients undergoing craniotomy

(1) Systemic analgesia should include paracetamol, NSAIDs administered pre-operatively or intra-operatively and continued postoperatively.
(2) Intra-operative dexmedetomidine infusion is recommended, as it is associated with reduced postoperative pain. Caution with regards of cardiovascular effects is warranted.
(3) Either incision-site infiltration or scalp nerve block is recommended as regional analgesic technique.
(4) Opioids should be reserved as rescue analgesia in the postoperative period.

Why was this guideline developed?

Craniotomy can be associated with intense postoperative pain and poorly controlled pain may aggravate neurosurgical comorbidities. The aim of this guideline is to provide clinicians with an evidence-based approach to pain management after craniotomy that should improve postoperative pain relief.

What other guidelines are available on this topic?

Recent publications tried to established protocols for pain management after craniotomy.[1,2] A Cochrane meta-analysis considers the preventive pharmacological interventions for post craniotomy pain.[3]

How does this guideline differ from other guidelines?

Two published pain management protocols have been established without systematic reviews of the literature.[1,2] The Cochrane meta-analysis only considered preventive pharmacological interventions.[3] The procedure-specific postoperative pain management (PROSPECT) approach to developing guidelines considers any type of intervention to alleviate pain, either preventive or curative. Moreover, the available evidence is critically assessed for current clinical relevance and the use of simple, nonopioid analgesics, such as paracetamol and NSAIDs as baseline analgesics is considered. This approach reports true clinical effectiveness by balancing the invasiveness of the analgesic interventions and the degree of pain after surgery while balancing efficacy and adverse effects.

Introduction

Pain after craniotomy can be intense and is often poorly managed.[4,5] Up to 90% of patients will experience pain after craniotomy and more than half of them report moderate to severe pain.[1,3,6] Pain after craniotomy is usually superficial with a somatic origin involving the scalp, pericranial muscles and soft tissue as well as dura mater.[7] Infratentorial procedures are associated with more severe pain than supratentorial procedures.[6] The severity of pain decreases with time, being more intense in the first two postoperative days.[6] Poorly controlled pain may increase morbidity and hospital length of stay. Pain-related systemic hypertension, agitation and vomiting can lead to intracranial hypertension and imitate, hide and even aggravate neurosurgical complications. Poorly controlled postoperative pain may also lead to prolonged recovery and chronic headaches.[1,3,8]

Guidelines regarding pain management after craniotomy are scarce. A recent systematic review of the literature from inception to 2018 assessed the efficacy of available pharmacological interventions to prevent pain after brain surgery.[3] With high-quality evidence, NSAIDs reduce pain score on first postoperative day. Dexmedetomidine, gabapentinoid, scalp nerve block (SNB) and incision-site infiltration (ISI) are effective at reducing pain up to 12 h postoperatively (low to moderate-quality evidence). SNB and dexmedetomidine may reduce additional analgesic requirement (low-quality evidence). However, this meta-analysis only considered preventive pharmacological intervention for pain management.[3] The PROSPECT Working Group is a collaboration of surgeons and anaesthetists working to formulate procedure-specific recommendations for pain management after common but potentially painful operations. The recommendations are based on a procedure-specific systematic review of randomised controlled trials (RCTs) and systematic review/meta-analyses. The methodology considers clinical practice, efficacy and adverse effects of analgesic techniques.[9]

The aim of this systematic review was to evaluate the available evidence for management of pain after craniotomy. The primary outcomes were effective reduction of postoperative pain scores. Other recovery outcomes, including adverse effects, were also assessed when reported in the literature and the limitations of the published data were reviewed. The ultimate aim was to develop recommendations for pain management after craniotomy according to the PROSPECT methodology.

Materials and methods

A review of RCTs and systematic reviews and meta-analyses published in English between January 2010 and June 2021 assessing analgesia after craniotomy was performed using MEDLINE (PubMed), EMBASE and Cochrane Databases. The search terms related to pain interventions for craniotomy included ('craniotom*' OR 'craniectom*' OR 'cranial surger*' OR 'endocranial surger*' OR 'cranial suture*' OR 'cranial resection*' OR 'brain surger*' OR 'brain resection*' OR 'cerebral surger*' OR 'cerebral resection*' OR 'head surger*' OR 'temporal surger*' OR 'temporal resection*' OR 'frontal surger*' OR 'frontal resection*' OR 'occipital surger*' OR 'occipital suture*') AND ('pain' OR 'pains' OR 'painful*' OR 'pain management' OR 'postoperative

pain' OR 'post operative pain' OR 'postoperative pain' OR 'analgesi*' OR 'anaesthe*' OR 'anesthe*' OR 'vas' OR 'visual analog*' OR 'vrs' OR 'verbal rating scale*' OR 'nrs' OR 'numerical rating scale*' OR 'pain rating' OR 'pain rating scale*' OR 'local infiltration*' OR 'topic infiltration*' OR 'infiltration*' OR 'NSAID' OR 'NSAIDS' OR 'Nonsteroidal antiinflammator*' OR 'Nonsteroidal antiinflammator*' OR 'Nonsteroidal anti inflammator*' OR 'Nonsteroidal anti inflammator*' OR 'cox2' OR 'cox-2' OR 'celecoxib' OR 'paracetamol' OR 'acetaminophen' OR 'clonidine' OR 'dexmedetomidine' OR 'opioid*' OR 'ketamine' OR 'corticosteroid*' OR 'gabapentin' OR 'pregabalin').

The RCTs that reported data pooled from patients undergoing other simultaneous surgical procedures were excluded, as were the RCTs evaluating combinations of different peri-operative interventions such as studies comparing enhanced recovery programmes to conventional care. The variability of definitions and protocols can make practical recommendations about a particular intervention impossible. Meta-analyses that reported data on mixed surgical procedures were only included when a sub-analysis on craniotomy was available. We used them to both identify missed RCTs and support our conclusions based on individual RCT data.

The following criteria were employed to assess the quality of eligible studies: allocation concealment of treatment assignment (A, adequate; B, unclear; C, inadequate; D, not used); statistical analyses and patient follow-up assessment (reported statistical analysis and follow-up >80%); and quality scoring using Jadad numerical score to assess randomisation (Supplemental Table 1, http://links.lww.com/EJA/A852).[9]

Data extraction and data analysis adhered to the PROSPECT methodology.[9] Pain intensity scores were used as the primary outcome. In this review, a change of more than 10 mm out of 100 mm on the visual analogue scale (VAS) or more than 1 out of 10 on a numerical rating score (NRS) was considered as clinically relevant. This change has been proposed as 'minimal clinically important difference' for acute pain management.[10] Secondary outcomes include cumulative 24-h opioid requirements, other supplementary analgesic use, opioid-related adverse events and patient-related outcomes.

We made recommendations according to PROSPECT methodology.[9] An analgesic intervention must be shown to be beneficial in at least two RCTs to be recommended. In addition, to ensure clinical relevance, the pertinence to current peri-operative practice is assessed. Likewise, we assess if the analgesic intervention would improve postoperative pain relief when added to the 'basic analgesic regimen' or would be beneficial if this regimen is not possible or is contra-indicated. The opioid-sparing effects of paracetamol and NSAIDs (termed as 'basic analgesic regimen') are well described for a wide range of surgical procedures.[9] The PROSPECT group assesses if the addition of an analgesic intervention would further improve pain relief when combined with these simple, effective, nonopioid analgesics. Furthermore, the balance between the invasiveness of the analgesic technique and the consequences of postoperative pain, and the balance between the analgesic efficacy and the adverse event profile of the analgesic technique are also considered.

The PROSPECT Working Group reviewed the proposed recommendations as well as the included evidence and a modified Delphi approach was used.[9] Five questions were asked of the working group about each recommendation: (1) Is the recommended intervention clinically relevant? (2) Does it add to the 'basic analgesic technique'? (3) Does the balance between efficacy and adverse effects allow recommendation? (4) Does the balance between invasiveness of the analgesic intervention and degree of pain after surgery allow recommendation? (5) Are the reasons for not recommending an analgesic intervention appropriate? Once a consensus was achieved, the lead authors drafted the final document, which was ultimately approved by the working group.

Results

A total of 126 studies assessing analgesic interventions were identified. The PRISMA flow chart summarising the search data is presented in Fig. 1. Ultimately, 53 RCTs and seven systematic reviews or meta-analyses were included for the final qualitative analysis. The characteristics of the included studies are presented in Supplemental Table 2, http://links.lww.com/EJA/A853 (recommended analgesic interventions) and Supplemental Table 3, http://links.lww.com/EJA/A854 (not recommended analgesic interventions).

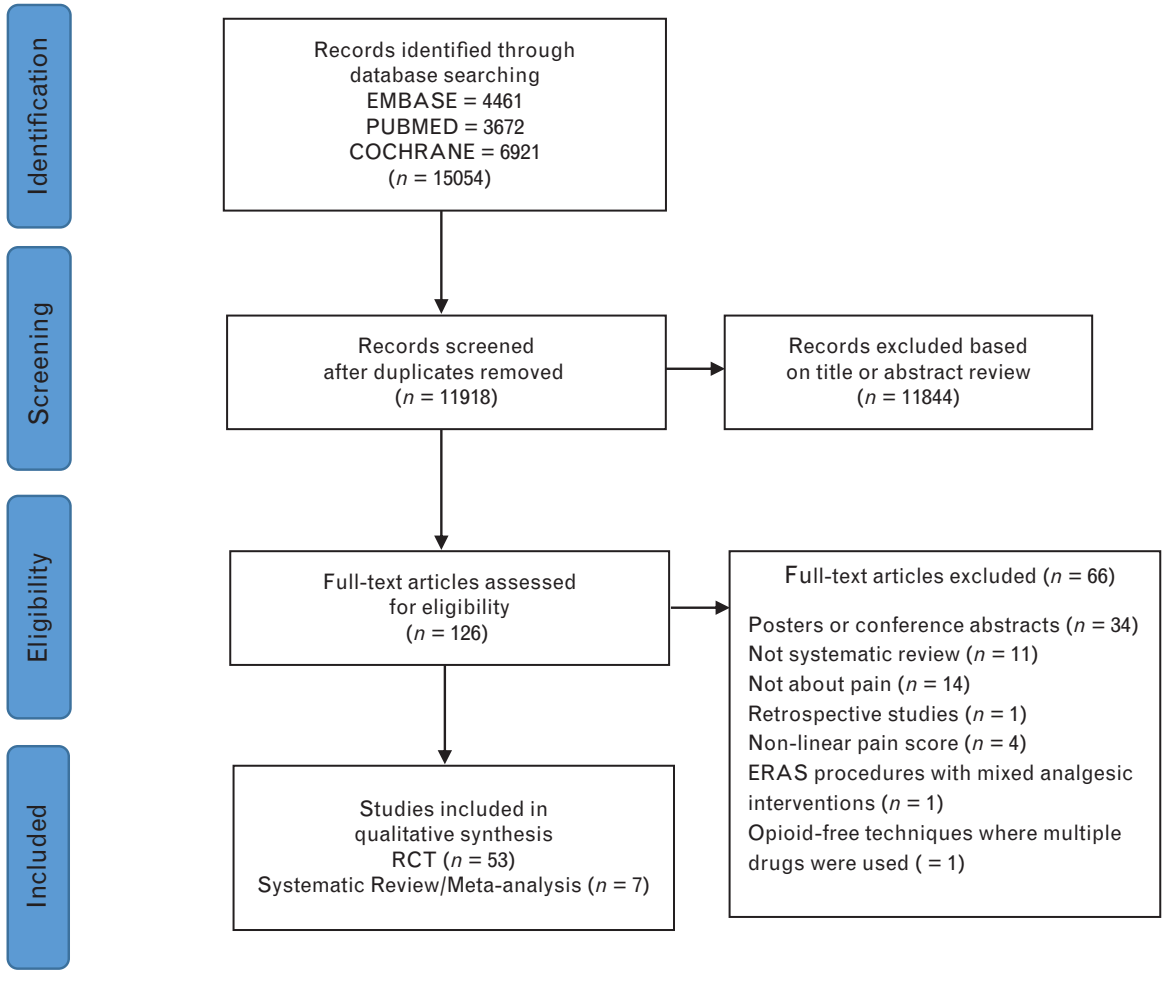
Pharmacological interventions

Systemic interventions

Paracetamol

Five RCTs have assessed the benefit of peri-operative paracetamol. In four RCTs, paracetamol administration was compared with placebo,[11–14] while one study compared three different analgesics (dexketoprofen, metamizole and paracetamol) with each other and with placebo.[15] Paracetamol reduced postoperative pain scores in three studies out of five but did not reduce postoperative opioid use.[11,12,15] In these three studies, paracetamol was used in combination with local infiltration of the incisional site and still demonstrated a reduction in postoperative pain.[11,12,15] In all studies, paracetamol was not combined with NSAIDs or COX-2 inhibitors. Four studies used paracetamol postoperatively, administered on scheduled basis.[11–13,15] In one study, paracetamol was only used intra-operatively, showing no difference in postoperative pain scores.[14]

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram.



None of the included studies reported significant differences in terms of opioids adverse events and patient-related outcomes.[11–15]

A meta-analysis of four RCTs ($n = 459$) showed no statistically significant difference in pain scores in the paracetamol group compared with placebo at different endpoint (0 to 6, 12, 24 and 48 h).[3] Another meta-analysis of five RCTs ($n = 515$) also found lower pain scores in the paracetamol group. Pooled results (any endpoint) indicated that paracetamol significantly decreased postoperative pain scores even though the effect was weak.[16]

NSAIDs

Six RCTs evaluated the efficacy of NSAIDs in craniotomy. One RCT compared NSAIDs with placebo,[17] two with paracetamol[18,19] and one with control (no medication).[20] Two studies compared different analgesics (dexketoprofen-metamizole-paracetamol and diclofenac-flupirtine) with each other and with placebo.[15,21] Five out of six studies showed positive analgesic effects compared with placebo[15,17,18,20,21] and an opioid-sparing effect was demonstrated in four studies.[18–21] Except for one study,[15] all provided paracetamol as basic analgesic and four studies used either scalp infiltration[15,17,20] or SNB[19] and still showed an analgesic effect of NSAIDs, except for the studies using SNB. Used as premedication, single-dose intra-operatively or postoperatively on a scheduled basis, diclofenac and dexketoprofen reduced postoperative pain scores.[18–21] A single intra-operative dose of parecoxib also provided significant analgesia but no opioid-sparing effect.[17]

Included RCTs reported no difference in opioid-related events and adverse events,[15,17–21] including postoperative bleeding.[20,21]

A systematic review and a meta-analysis evaluated the analgesic effects of NSAIDs in brain surgery.[3,22] NSAIDs provided satisfactory pain relief without adverse events (including bleeding) (three RCTs, $n = 667$ patients).[22] A meta-analysis of eight RCTs ($n = 742$ patients) demonstrated that, compared with placebo, NSAIDs provided

superior pain relief at 6, 12 and 24 h after surgery along with an opioid-sparing effect. In addition, postoperative nausea and vomiting (PONV) were less observed in NSAIDs groups.[3]

Flupirtine

In a three-armed RCT, flupirtine showed similar analgesic and opioid-sparing effects compared with diclofenac, being always superior to placebo. Paracetamol was used as baseline analgesia in all studied groups. Authors reported no difference in adverse events.[21]

Metamizole

When given three times daily, compared with placebo, metamizole neither reduced pain scores nor opioid consumption. Authors reported no difference in adverse events.[15]

Opioids

Two RCTs compared the analgesic efficacy of postoperative fentanyl administered either by patient-controlled analgesia (PCA) or as needed.[23,24] Patients using PCA achieved better analgesia but consumed more opioids. Baseline analgesia was used in all groups.[23,24] A three-armed RCT compared postoperative continuous sufentanil infusion, subcutaneous morphine and intravenous (i.v.) paracetamol for pain management.[25] Sufentanil infusion reduced pain scores compared with paracetamol. There was no difference in pain scores when comparing morphine with sufentanil or with paracetamol. More patients in the group paracetamol required additional morphine but cumulative morphine equivalent dose was not assessed.[25] One RCT showed that patients achieved better pain relief in the first 12 postoperative hours with the PCA pump with morphine compared with i.v. paracetamol and dexketoprofen.[26] Oral tramadol added to baseline analgesia provided both better pain relief and opioid-sparing effects compared with placebo.[27] Oral oxycodone and oral codeine showed similar results for postoperative pain and opioid consumption in the presence of baseline analgesia, paracetamol and ISI.[28]

One RCT reported more PONV in opioid groups,[25] while others showed no difference.[23,24,26,28] Patient-related outcomes were similar amongst groups, especially sedation score, Glasgow coma scale and respiratory depression.[23–26,28]

One systematic review concluded that opioid offered better pain relief at the cost of more PONV (five RCTs, $n = 316$).[22]

Gabapentinoids

Two placebo-controlled RCTs assessed the efficacy of premedication with gabapentin 600 mg the evening before and 2 h before surgery,[29] and pregabalin 75 or 150 mg 1 h before surgery,[30] without differences in postoperative pain scores. Pregabalin demonstrated opioid-sparing effect while gabapentin did not.[29,30] One study reported decreased vomiting but increased sedation score, particularly at 2 h postoperatively.[29] None of these studies used basic analgesia.

One placebo-controlled RCT evaluated the beneficial effects of peri-operative pregabalin (150 mg the night before, 1.5 h before surgery, 2 h after surgery and then twice daily for the next 72 h) on postoperative analgesic requirements and pain scores. Pain scores were lower in the pregabalin group but were only statistically significant at ICU arrival. Less patients in the pregabalin group needed postoperative opioids, vomited and needed an antiemetic drug. Baseline analgesia was a combination of nonopioid drugs and weak opioid analgesic (paracetamol, diclofenac, tramadol) and also included ISI.[31]

Dexmedetomidine

Three placebo-controlled RCTs investigated the effect of intra-operative infusion of dexmedetomidine (DEX) ranging from 0.2 to 0.5 $\mu g\,kg^{-1}\,h^{-1}$.[32–34] Postoperative pain scores were lower in the DEX group up to 12 h postsurgery, with reduced opioid consumption. Basic analgesia with either paracetamol or NSAIDs was provided in all three RCT. In another study, intra-operative low-dose (0.4 $\mu g\,kg^{-1}$) and medium-dose (0.8 $\mu g\,kg^{-1}$) DEX bolus decreased postoperative pain scores in PACU and opioid rescue doses compared with placebo. However, hypertension occurred during the DEX infusion, which required nicardipine administration in up to 90% of the patients in the medium-dose group. Conversely, emergence tachycardia and hypertension were less likely in both DEX group compared with control group.[35]

Two RCTs compared intra-operative DEX infusion versus opioids (remifentanil and fentanyl) infusion. Patients receiving the DEX infusion experienced lower pain score and consumed less opioid in the first 90 min postoperatively.[36] However, in a pilot study, DEX infusion showed no difference in postoperative pain scores when compared with fentanyl infusion.[37]

With the exception of one study,[35] there was no significant difference in haemodynamic variables.[32–34,36,37] One RCT reported faster emergence from general anaesthesia in its remifentanil group compared with the DEX group.[36] Another reported lower Ramsay sedation score in the DEX group at 2 and 4 h.[34] Two RCTs reported no significant difference in emergence time or postoperative sedation.[32,33] Three RCTs reported no difference in PONV,[32,34,35] while one showed lower PONV scores in the DEX group.[33]

One systematic review and one meta-analysis have analysed the peri-operative use of DEX for pain control after craniotomy. The former reported short-term analgesic efficacy combined with opioid-sparing effect during PACU stay and up to 12 h postoperatively (three RCTs,

$n = 267$).[22] The latter included two RCTs ($n = 128$) that found intra-operative DEX infusion reduced both pain up to 12 h postoperatively and postoperative opioid requirements. Other outcomes (nausea and vomiting, hypotension) were imprecise.[3]

Magnesium sulphate

A placebo-controlled RCT investigated the intra-operative administration of magnesium sulphate ($MgSO_4$) 50 mg kg^{-1} bolus followed by continuous infusion of 25 mg kg^{-1} h^{-1} and showed reduced pain scores and lower opioid requirements during ICU stay in first postoperative 24 h. Adverse events were not observed.[38]

Lidocaine

In one study, continuous intra-operative infusion of lidocaine improved pain control for 24 h postoperatively and reduced postoperative fentanyl consumption; however, the differences in pain scores were not clinically significant beyond the first hour. NSAIDs were given when needed but use of local block or wound infiltration was not reported.[38]

Sumatriptan

Given postoperatively in one study when patients complained of headache, subcutaneous sumatriptan reduced headache pain scores but not incisional surgical pain scores. Sumatriptan did not show any opioid-sparing effect. PONV occurrence was similar amongst groups and no adverse events were noted.[39]

Vitamin D

Pre-operative vitamin D supplementation did not show any effect on postoperative pain relief or on opioid consumption when compared with placebo. Adverse events were not reported.[40]

Regional anaesthesia and analgesia

Scalp nerve block

Nine RCTs considered the use of presurgical SNB.[41–49] Eight out of the nine demonstrated that single injection SNB reduced pain scores, with a lasting effect from 2 to 48 h postoperatively, compared with placebo.[41–47,49] SNB also reduced postoperative opioid consumption in four studies.[41,46,47,49] These analgesic effects were also present in RCTs using basic analgesics.[45,47,49]

Another RCT compared SNB with intra-operative DEX infusion. The pain scores were lower up to 2 h postoperatively, but the differences were not clinically significant.[48] An RCT compared presurgical SNB to postsurgical SNB and showed no differences.[50] Two placebo-controlled RCTs studied the effects of postsurgical SNB on pain score.[51,52] Both used basic analgesics and found a pain score reduction in the first 2 postoperative hours,[51] even up to 48 h,[52] but postoperative opioid consumption was lower in only one study.[52]

PONV occurred less often in SNB group in two RCTs,[41,52] while five RCTs reported similar opioid-related outcomes between study groups.[42–44,46,51] When reported, authors did not observe major adverse events.[41–45,48,50–53]

All included studies used long-lasting local anaesthetics, such as levobupivacaine (5.0 to 7.5 mg ml^{-1}, five RCTs), bupivacaine (2.5 mg ml^{-1}, five RCTs) or ropivacaine (2.0 to 7.5 mg ml^{-1}, two RCTs). Lidocaine was considered in a mixture with bupivacaine 5 mg.ml^{-1} in one study.[41–52]

Two systematic reviews and three meta-analyses have assessed the analgesic effects of SNB when compared with placebo or control.[3,53–56] The two systematic reviews (two RCTs included, $n = 70$[53] and five RCTs included, $n = 237$[55]) concluded that SNB provided analgesia for a few hours postoperatively while asking for larger trials.[53,55] In one meta-analysis (seven RCTs), a reduction in pain scores during the first 6 to 8 postoperative hours (six RCTs, $n = 284$) and a lower postoperative opioid requirement (six RCTs, $n = 239$) were highlighted. Further, in a subgroup analysis, presurgical SNB provided better pain control at 1, 2 and 4 h postoperatively and the postsurgical analgesic effect lasted up to 12 h (four RCTs, $n = 150$).[56] Another meta-analysis (12 RCTs) reported significant analgesic effects for the first 6 h (10 RCTs, $n = 414$), at 12 h (eight RCTs, $n = 294$), at 24 h (nine RCTs, $n = 433$) and at 48 h (four RCTs, $n = 135$). SNB also provided significant opioid-sparing effect (seven RCTs, $n = 341$).[3] One meta-analysis (10 RCTs, $n = 551$) showed similar positive results during the first 6 h postoperatively. Likewise, SNB reduced total opioid consumption within the first 24 h.[54]

Incision-site infiltration

A placebo-controlled RCT showed an opioid-sparing effect of ISI with ropivacaine 5 mg.ml^{-1} but without reduction of pain scores.[57] In two RCTs, presurgical ISI with bupivacaine (5 and 7.5 mg ml^{-1}) offered better pain control for the first 4 h postoperatively when compared with placebo but was less effective when compared with SNB. ISI reduced opioid consumption within 24 h compared with placebo in one of those two studies, showing no difference when compared with SNB,[46] although it was less effective than SNB in another study.[41] A RCT compared especially ISI and SNB with a mixture of bupivacaine 5 mg.ml^{-1} and lidocaine 20 mg.ml^{-1} and showed better pain control in the PACU with ISI but less opioid-sparing effect.[58] Finally, when comparing the timing of ISI, preincisional infiltration with a mixture of ropivacaine 10 mg.ml^{-1} and lidocaine 20 mg.ml^{-1} provided better pain relief than postincisional infiltration for the first 4 h postoperatively and reduced cumulative opioid consumption within 24 h after surgery.[59] Only two of the five ISI studies used basic analgesics.[58,59]

Two RCTs reported reduced PONV in ISI groups,[41,57] while two other RCTs showed no difference in opioid-related outcomes.[46,59]

Two systematic review and one meta-analysis have reviewed the effects of ISI versus placebo or control.[3,22,53] ISI may be effective in the first few hours postoperatively, but its duration of action was variable (five RCTs, $n = 249$), at least when compared with SNB, which seems to be longer lasting and provides superior analgesia.[53] Another systematic review included three RCTs ($n = 138$) studying either SNB (two RCTs) or ISI (one RCT), and suggested, without specifying, that both techniques may provide adequate analgesia in the early postoperative hours.[22] Conversely, scalp infiltration showed significant efficacy only at 12 h (seven RCTs, $n = 309$) and at 48 h (three RCTs, $n = 128$) in a meta-analysis, but the differences in pain scores were not significant in the first 6 h (nine RCTs, $n = 475$).[3]

Bilateral maxillary block and superficial cervical plexus block

Both peripheral nerve blocks failed to demonstrate any benefits in terms of pain relief and opioid consumption.[60,61]

Hyaluronidase as adjuvant

In one study, hyaluronidase added to the local anaesthetic mixture reduced the pain scores in the first 8 postoperative hours and decreased the need for ketorolac used as rescue analgesia.[62]

Dexamethasone as adjuvant

Added to local anaesthetic mixture for presurgical ISI, dexamethasone reduced pain scores from 8 to 72 h with opioid-sparing within 48 h after surgery.[63]

Alpha-adrenergic agonist as adjuvant

Three RCTs evaluated the analgesic effect of an α-adrenergic agonist added to the local anaesthetic mixture.[64–66] Dexmedetomidine added to SNB and ISI improved the analgesic effect in one out of two studies, and the effect was greater when added to SNB compared with ISI.[65] The addition of clonidine to the local anaesthetic mixture for SNB reduced pain scores at 24 h postoperatively and was associated with postoperative opioid-sparing.[66] The two positive studies also included basic analgesic (paracetamol).[65,66] One RCT reported higher postoperative sedation score in the DEX group without it being excessive (Ramsay score >3).[65]

Nonpharmacological interventions

Acupuncture

Three RCTs ($n = 286$) compared different types of acupuncture and all showed an analgesic effect.[67–69] Multipoint acupuncture also provided an opioid-sparing effect in one study.[69] No RCT used basic analgesic and one study used ISI in acupuncture and placebo groups.[67]

Discussion

This review aimed to synthesise the available evidence on pain management after craniotomy under general anaesthesia. High-quality postoperative pain management ensures optimal recovery after neurosurgical procedures. Poorly controlled pain and adverse effects related to the use of analgesics, specifically opioids-induced nausea, vomiting and sedation, are unwanted. Because opioids can interfere with early neurologic examination, they should be used as rescue analgesia in case of severe pain and not as routine analgesia.[1]

Peri-operative paracetamol and NSAIDs or COX-2 selective inhibitors are considered as the 'basic analgesic regimen'.[9] Paracetamol has a weak analgesic and opioid-sparing effect. Both single dose and administration on a scheduled basis with NSAIDs or COX-2 selective inhibitors provide significant analgesic and opioid-sparing effects. NSAIDs in combination with paracetamol results in enhanced analgesia.[17,20,21] Concern about NSAIDs complications, such as intracranial bleeding and bone healing impairment, is unwarranted. A recent meta-analysis (74 studies, including 41 RCTs) concluded that NSAIDs are not associated with clinically important bleeding. These results were consistent across various types of NSAIDs and surgical procedures.[70] In a retrospective study ($n = 452$), continuing acetyl salicylic acid was not associated with an increased risk of peri-operative complications, including bleeding.[71] A cohort study showed an adjusted estimate risk of symptomatic bleeding very close to null effect, but the width of the confidence interval prevented a conclusion on the safety of ketorolac.[72] Similarly, two retrospective studies on children concluded that short-term NSAID therapy was not associated with an increased risk of haemorrhage.[73,74] Currently, there is no evidence that potential side effects of NSAIDs outweigh their benefits, except when contra-indicated, such as in patients with significant renal impairment. Therefore, we recommend paracetamol and NSAIDs/COX-2-selective inhibitors as basic analgesia after craniotomy.

Intra-operative DEX has shown a positive effect on both pain and opioid consumption when compared with either placebo or opioids (remifentanil, fentanyl), and also when basic analgesia was used.[32–37] Some concerns about haemodynamic events and sedative effects with delayed postoperative evaluation have been raised[35,36] despite the use of low doses.[32–37] A systematic review of three RCTs emphasised the opioid-sparing effect but warned of delayed recovery and longer discharge time from the PACU.[22] In summary, the PROSPECT group recommend its use for pain relief after craniotomy with the proviso that potential adverse events including haemodynamic effects and sedation can influence recovery.

In addition to systemic analgesics, regional analgesic techniques such as SNB and ISI are effective. Ten RCTs have demonstrated the analgesic efficacy of SNB, administered either pre-operatively or postoperatively, when compared with placebo or no block.[41–47,49,51,52] These findings are supported by previous systematic reviews and meta-analysis, with an analgesic effect in the first 6 postoperative hours and a moderate opioid-sparing effect.[3,53–56] The risks associated with SNB include local anaesthetic toxicity, transient facial nerve palsy and inadvertent subarachnoid injection.[1] ISI is widely used for craniotomies. Three RCTs showed positive effects on both pain scores and opioid consumption, but only one RCT used baseline analgesia.[41,46,59] Either SNB or ISI with long-acting local anaesthetic is recommended, but ISI may have a more limited duration of analgesia than SNB, although there are not enough studies comparing the two techniques to recommend one over the other. Considering the lack of data on the combination of techniques and high vascularisation of the scalp, combining the two techniques is not recommended due to the risk of local anaesthetic toxicity. Adding α2-adrenergic agonists (clonidine and dexmedetomidine) as adjuvants to regional techniques has been studied, but evidence for increased analgesia after local administration is minimal,[65,66] so this cannot be recommended due to limited evidence.

Two RCTs studied the effects of intra-operative multipoint electro-acupuncture, and one explored the used of postoperative single point acupuncture. All the studies showed positive results on postoperative pain. However, none considered basic analgesics.[67–69] Surprisingly, only one study demonstrates an effect on PONV, in contrast with the current literature on acupuncture and electro-acupuncture.[75–78] Acupuncture is recommended if basic analgesics cannot be used. However, acupuncture may be impractical, and its application may generate a risk of infection.

Gabapentinoids have analgesic effects after craniotomy, but none of the studies used basic analgesics: paracetamol and/or NSAIDs.[29,30] Therefore, as stated in a recent review, the role of gabapentinoids in acute postcraniotomy pain management remains unclear.[22] More importantly, gabapentinoids have concerning side effects such as sedation, blurred vision and dizziness.[79] Also, FDA has recently warned of the risks of respiratory depression.[80] For these reasons, despite evidence of a minimal analgesic effect of short duration, gabapentinoids are not recommended.

We did not find any study that examined the role of i.v. ketamine for pain management after craniotomy, and nor did any systematic review.[81] We did not find any study assessing the role of i.v. dexamethasone for pain management after craniotomy. However, i.v. dexamethasone is often used in intracranial surgery to reduce tumour-associated oedema and to prevent PONV.[82] In addition, i.v. dexamethasone can reduce postoperative pain score and opioid consumption.[83–85] Caution is warranted in patients with glucose intolerance.

The limitations of this review are related to those of the included studies. There was considerable heterogeneity between studies in terms of dosing regimens, methods of administration, use of basic analgesics in the control groups and time-points of pain measurement. The RCTs included evaluated pain at different time intervals, and expected patients to understand and evaluate their pain. Patients with central nervous system impairment from operation-related complications were managed with re-operation and thus excluded. As many of the included studies suffered from small sample size, it is difficult to draw firm conclusions regarding the side effect profile of the proposed interventions. Most studies did not include basic analgesics (paracetamol and NSAIDs) making it unclear whether an effective intervention would remain effective if basic analgesia was administered. Furthermore, although the PROSPECT initiative promotes multimodal, nonopioid analgesic strategies and modern perioperative care, only a few studies applied real multimodal analgesic regimens or mentioned the application of enhanced recovery (ERAS) protocols.[9] A recent systematic review identified 17 complete ERAS protocols published for elective craniotomy, demonstrating positive results in different outcomes such as postoperative pain control, reduced length of stay and costs.[86] At present, studies investigating ERAS protocols in cranial surgery remain scarce and only three RCTs could be included in two recent systematic reviews.[87,88] These studies demonstrate the feasibility of enhanced recovery after brain surgery, but the benefits need to be clarified.

In summary, our review has identified an analgesic regimen for optimal pain management after craniotomy (Table 1). We suggest that peri-operative pain management for craniotomy includes, unless contraindicated, paracetamol combined with NSAID or COX-2 selective, administered either pre-operatively or intra-operatively and continued postoperatively. In addition, either ISI or SNB is recommended. These blocks may be administered before incision or at the end of the procedure. Intra-operative dexmedetomidine infusion is recommended, carefully considering the dose-dependent haemodynamic

Table 1 Analgesic interventions that are recommended for pain management in patients undergoing craniotomy

Pre-operative/Intra-operative
Paracetamol
NSAIDs
Either scalp block or incision-site infiltration
Intravenous dexmedetomidine infusion
If basic analgesia is not possible, acupuncture
Postoperative
Paracetamol and NSAIDs
Opioids as rescue

Table 2 Analgesic interventions that are not recommended for pain management in patients undergoing craniotomy

Intervention	Reason for not recommending
Flupirtine	Limited procedure-specific evidence
Metamizole	Lack of procedure-specific evidence
Gabapentinoids	Additional benefit is questionable and concerns about side effects
Intra-operative use of magnesium sulphate	Limited procedure-specific evidence
Intra-operative use of lidocaine	Limited procedure-specific evidence
Postoperative subcutaneous sumatriptan	Lack of procedure-specific evidence
Pre-operative vitamin D	Lack of procedure-specific evidence
Bilateral maxillary block	Lack of procedure-specific evidence
Superficial cervical plexus block	Lack of procedure-specific evidence
Hyaluronidase as adjuvant	Limited procedure-specific evidence
Dexamethasone as adjuvant	Limited procedure-specific evidence
Clonidine as adjuvant	Limited procedure-specific evidence
Dexmedetomidine as adjuvant	Limited procedure-specific evidence

side effects. Also, acupuncture may be considered if basic analgesic is not possible. Systemic opioids should be reserved as rescue analgesics in the postoperative period. Despite the lack of specific evidence, we also recommend i.v. dexamethasone. We also identified analgesic interventions that are not recommended for pain management in patients undergoing craniotomy, listed in Table 2. Future high-quality studies are needed to clarify the efficacy of recommended approaches in the context of an enhance recovery pathway.

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