

Review Article

Designing a pain management protocol for craniotomy: A narrative review and consideration of promising practices

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Abstract

Background: Craniotomy is a relatively common surgical procedure with a high incidence of postoperative pain. Development of standardized pain management and enhanced recovery after surgery (ERAS) protocols are necessary and crucial to optimize outcomes and patient satisfaction and reduce health care costs.

Methods: This work is based upon a literature search of published manuscripts (between 1996 and 2017) from Pubmed, Cochrane Central Register, and Google Scholar. It seeks to both synthesize and review our current scientific understanding of postcraniotomy pain and its part in neurosurgical ERAS protocols.

Results: Strategies to ameliorate craniotomy pain demand interventions during all phases of patient care: preoperative, intraoperative, and postoperative interventions. Pain management should begin in the perioperative period with risk assessment, patient education, and premedication. In the intraoperative period, modifications in anesthesia technique, choice of opioids, acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), regional techniques, dexmedetomidine, ketamine, lidocaine, corticosteroids, and interdisciplinary communication are all strategies to consider and possibly deploy. Opioids remain the mainstay for pain relief, but patient-controlled analgesia, NSAIDs, standardization of pain management, bio/behavioral interventions, modification of head dressings as well as patient-centric management are useful opportunities that potentially improve patient care.

Conclusions: Future research on mechanisms, predictors, treatments, and pain management pathways will help define the combinations of interventions that optimize pain outcomes.

Key Words: Analgesia, chronic pain, craniotomy, local anesthetics, neurosurgery

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INTRODUCTION

Enhanced recovery after surgery (ERAS) protocols are designed to optimize outcomes, patient satisfaction, and reduce health care costs.^[45] Development of ERAS pathways requires standardized protocols for key elements of perioperative care.^[128,130] The protocols are developed to accommodate local circumstances and expertise. The project involves a multidisciplinary team, starts with

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process mapping, a review of the evidence supporting each care item and ends with consensus for a consistent clinical approach.^[100] These protocols exist for a number of surgical subspecialties, but are an emerging area of interest for neurosurgical care.^[25]

Standardization of pain management is a key element of enhanced recovery protocols. Pain after craniotomy is a common occurrence^[96] and associated with poor outcomes.^[6,72] Both facts provide impetus to define the best options for management. A review of craniotomy pain management detailing all the considerations for each phase of care is currently unavailable. The goal of this review is to create an alembic for the design of a standardized pain management protocol for craniotomy in the context of the development of an ERAS protocol for neurosurgery.

Search strategy

This work is based on pertinent literature published from 1996, the date of a pivotal pilot study on craniotomy pain,^[11] until 2017, by searching Pubmed, Cochrane Central Register, and Google Scholar using a combination of medical subject headings (MeSH) terms and free-text words to identify manuscripts related to postcraniotomy pain and ERAS protocols. Due to the many aspects of perioperative care covered in this review, a formal literature search was not done.

Overview of eras approach to pain management

ERAS protocols divide the key components of perioperative care according to phase of care: preoperative, intraoperative, and postoperative interventions.^[100] Preoperative interventions aim at optimizing the patient for surgery, including patient education, risk assessment, and medication. Intraoperative interventions target the reduction of surgical stress response, the selection of anesthesia technique, regional anesthesia, multimodal analgesia, and minimal access surgery. Postoperative interventions aim at rehabilitation and return to normal diet and activity; this involves pain assessment, targeting effective pain management to facilitate early mobilization and using multimodal pain strategies.

Significance of poscraniotomy pain

Pain after craniotomy is moderate to severe in up to 90% of patients within the first several days after the procedure.^[96] As many as 30% of patients develop chronic headache.^[107] Craniotomy is a relatively common surgical procedure. It is performed for many indications, including biopsy or resection of intracranial mass lesions, treatment of intracranial vascular pathologies, treatment of epilepsy, and management of trauma. Although the total number of craniotomies performed annually in the United States is difficult to estimate, in 2004, 2007 the estimated number of craniotomy procedures performed annually in the United States were as follows: craniotomy for tumor (70,849), craniotomy for vascular surgery (2237)

and craniotomy for other purposes (56,405).^[88] Poorly controlled pain has potentially devastating consequences such as postoperative intracranial hemorrhage due to sympathetically induced arterial hypertension^[59] as well as intracranial hypertension due to agitation or respiratory depression. These complications prolong hospital stay,^[6,72] increase mortality,^[6] and health care costs.^[72] Finally, neurosurgical patients form a group in which analgesic regimens used for treating acute pain are particularly constrained by concerns about effects on coagulation and side effects such as sedation, miosis, and nausea and vomiting that could mask signs of intracranial catastrophe, delay postoperative evaluation, and precipitate costly tests.

Origin of postcraniotomy pain

Innervation of the scalp is derived from cranial nerves and dorsal and ventral spinal rami. Branches of the ophthalmic division of the trigeminal nerve innervate the forehead. Branches of the mandibular and maxillary divisions of the trigeminal nerve innervate the skin of the temple. The greater occipital nerve innervates the posterior scalp and the lesser occipital nerve innervates the skin behind the ear. The dura is innervated by branches of the trigeminal nerve, ventral and dorsal rami of the cervical nerves, branches of the vagus, and hypoglossal nerves. The innervations for the various regions of the cranial dura mater are summarized in Figure 1. Sources of postcraniotomy pain include tissue injury (scalp, cranial muscles soft tissue, and dura mater) and nerve disruption, traction, entrapment, and compression. Comprehensive reviews of scalp and dura sensory innervation are available.^[19,22]

Characteristics and time course

Acute postcraniotomy pain (ACP) is predominantly located to the area of incision, around occipital region and neck, and mainly involves pericranial muscle and soft tissues.^[11,74,86] It is described as “tensive,” “pulsating and pounding,” “dull ache or pressure,” or “steady and continuous.”^[11,86]

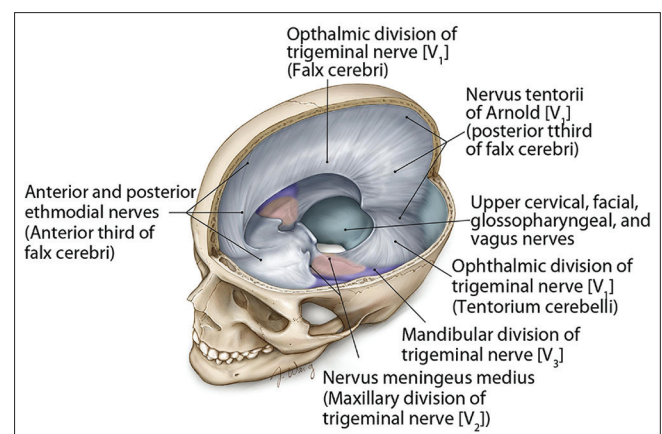


Figure 1: Summary of the innervations for the various regions of the cranial dura mater. (Reprinted with permission^[66])

Time-intensity curves showed that postcraniotomy pain is greatest in the first 48 h after surgery.^[11,42,72,96] The incidence of moderate to severe pain in fifteen studies evaluating the intensity of postcraniotomy pain on day one and two is presented in Table 1. A large number of patients experience acute moderate to severe pain despite the analgesia provided. This information, which includes recent experience from major neurosurgical centers, demonstrates the current opportunity for improving treatment of acute postcraniotomy pain.

Surgical procedures and their concomitant procedure specific pain syndromes are well recognized,^[64] chronic postcraniotomy pain (CCP), defined as pain that persists for more than 2–3 months after surgery,^[34] affects up to one-third of patients.^[80,107] Surgical incision and other perioperative events may induce prolonged changes to the central nervous system which, consistent with the neuromatrix model of pain,^[80] later contributing to chronic pain and headache.

Ten studies that evaluated the incidence of CCP were identified and summarized in Table 2.

Risk factors

Patient related risk factors

Independent predictors of severe postoperative pain after general anesthesia for various types of surgery are: younger age, female gender, level of preoperative pain, incision size, and type of surgery.^[61] The same trends are seen in postcraniotomy patients. Female^[11,18,42,107] and

younger patients^[11,85,129] have the highest incidence of pain, consistent with an increased reported sensitivity to pain in women.^[126] The probability of experiencing postcraniotomy pain is reduced by 3% for each additional year of life.^[85] Older patients may be more tolerant to pain,^[49,131] or alternatively, age-related tolerance may reflect differences in pharmacokinetics in this population. These patient-related factors are not uniformly accepted with regard to postcraniotomy pain as some studies show opposite results: namely that age, sex, and also the American Society of Anesthesiologists Physical Status Classification are not predictive of pain character or intensity.^[67] Neurosurgical patients have high levels of anxiety.^[97] Anxiety, depression, and preoperative pain are also possible risk factors for postcraniotomy pain.^[67,105,107]

Surgical procedure related risk factors

Craniotomy site may be a determinant for the type and severity of postoperative pain after neurosurgery.^[47,85] Patients who underwent infratentorial procedures have more pain than those submitted to a supratentorial approach.^[42,56] The subtemporal and suboccipital surgical routes yielded the highest incidence of postoperative pain.^[11] Frontal craniotomy is associated with lower pain scores and a significantly lower consumption of opioid analgesics.^[129] The relationship between craniotomy location and pain intensity may be explained, at least in part, by the anatomical location of pericranial muscles. The amount of postoperative pain may depend on the extent of muscle damage/muscle reflection in the operative

Table 1: Incidence of moderate to severe postcraniotomy pain (only studies that included pain scores and percentage of patients studied are included)

Postoperative day	Pain score (moderate 4-6; severe 7-10)	Incidence of Pain %	Number of patients studied	Type of study	Year	Reference
1	Mod	69	187	Case-series	2007	[42]
	Mod	44	243	Case-series	2010	[85]
	Mod	60	52	RCT	2015	[120]
	Mod	29	52	Case-series	1996	[101]
	mod-sev	38	59	Case-series	2013	[47]
	mod-sev	40	37	Case-series	1996	[11]
	mod-sev	77	40	RCT	2016	[77]
	mod-sev	24	91	Case-series	2013	[91]
	mod-sev	43	108	Case-series	2012	[18]
	mod-sev	40	79	Case-series	2007	[108]
	mod-sev	20-70	30	RCT	2001	[89]
	mod-sev	84	52	Cohort study	2003	[56]
	Sev	22-37	380	RCT	2012	[20]
	Sev	37	52	Case-series	1996	[101]
2	Sev	11	243	Case-series	2010	[85]
	mod-sev	40	37	Case-series	1996	[11]
	mod-sev	48	187	Case-series	2007	[42]
	mod-sev	29.2	91	Case-series	2013	[91]
	mod-sev	76	299	Case-series	2007	[129]
	mod-sev	93	40	Case-series	2005	[96]

Table 2: Incidence of chronic postcraniotomy pain (CCP)

Time-line	Incidence of CCP %	Number of patients studied	Diagnosis	Procedure	Type of study	Year	Reference
2 months	8-56	52	Tumor	Supra- and infratentorial craniotomy	RCT	2009	[7]
3 months	23	331	Acoustic neuroma	Infratentorial craniotomy	Case-series	1993	[50]
	34	155	Vestibular schwannoma	Infratentorial craniotomy	Case-series	2003	[112]
6 months	29.3	79	Aneurysm	Supratentorial intracranial	Case-series	2008	[107]
	13.1	320	Microvascular decompression	Infratentorial craniotomy	Case-series	1999	[75]
> 1 year	26	52	Acoustic neuroma	Infratentorial craniotomy	Cohort study	1996	[109]
	11.9	126	Epilepsy	Supratentorial intracranial	Case-series	2000	[63]
	16	331	Acoustic neuroma	Infratentorial craniotomy	Case-series	1993	[50]
	17	52	Acoustic neuroma	Infratentorial craniotomy	Cohort study	1996	[109]
	40	251	Vestibular schwannoma	Infratentorial craniotomy	Case-series	2000	[74]
	23	48	Acoustic neuroma	Infratentorial craniotomy	Case-series	1999	[86]
	27.2	228	Tumor	Infratentorial craniotomy	Case-series	1998	[48]
2 years	9	331	Acoustic neuroma	Infratentorial craniotomy	Case-series	1993	[50]
	27.1	251	Vestibular schwannoma	Infratentorial craniotomy	Case-series	2000	[74]

approach rather than the surgical location relative to the tentorium.^[85] Studies are contradictory regarding tumor size and prediction of postoperative pain.^[86,105]

Risks factors for chronic postcraniotomy pain

CCP severity and incidence is greater after infratentorial procedures than supratentorial procedures [Table 2].^[17,29,48,51,109,113,114,121] Several mechanisms for development of CCP are hypothesized, these include the possibility of adhesions (between dura and bone or muscle, and possibly between dura and brain), traction on the dura when the bone is not replaced,^[113,114] disturbance to the temporalis muscle and suboccipital musculature,^[114] peripheral nerve entrapment,^[23] aseptic meningitis,^[17] or, rarely, cerebrospinal fluid leakage.^[33]

Although no known surgical maneuver effectively prevents CCP, current recommended practice targets the restoration of muscular function, the rigid fixation of bone flaps, and cranioplasty in large craniotomies, the meticulous closing of the dura without tension, and the assiduous removal of blood and bone dust from intracranial contents.

The treatment of acute postcraniotomy pain has implications for long-term recovery: the severity of acute postsurgical pain predicts the incidence of chronic postsurgical pain after a number of surgical procedures.^[117] Likewise, regional infiltration with ropivacaine reduced the incidence of persistent and neuropathic pain two months after craniotomy, suggesting that mitigating acute postcraniotomy pain may help diminish the possibility of chronic postcraniotomy pain.^[7]

Perioperative interventions to improve pain experience after craniotomy

Strategies to ameliorate craniotomy pain demand interventions at all phases of patient care, these

include: education, risk stratification, pain consultation, multimodal analgesia, and nonpharmacological and bio-behavioral interventions. Multimodal analgesia, the gold standard for management of perioperative pain, is an approach that combines treatments with additive or synergistic effects, reducing opioid consumption, controlling side effects, and improving overall outcomes. Tables 3 and 4 provide a summary of the information presented about interventions and the components of multimodal analgesia, including oral and intravenous medications, and regional anesthesia.

Preoperative interventions

Preoperative risk assessment

Identifying high-risk patients (anxiety, depression, and chronic pain) may improve pain management. The benefits include improved multidisciplinary communication about potential pain outcomes, risk adjusted therapeutic interventions and optimization or protocol variation based on risk assessment, and triggering pain consultation or behavioral cognitive intervention.^[21] The procedure-specific benefit with regard to pain outcomes is not yet available.

Preoperative education

Surgical patients are concerned about pain and value content and communication about their pain experience.^[62] Educational material such as information about anticipated pain, treatment options, and side effects of pain medications may improve patient's pain experience.^[26,68,133] Although such outcome is not confirmed for all neurosurgical patients, it is a recommended component of enhanced recovery for oncological craniotomy.^[45]

Preoperative medication

Enhanced recovery protocols endorse standardized preoperative administration of oral medications

Table 3: Perioperative interventions

Preoperative period	Intraoperative period	Postoperative period
<ul style="list-style-type: none"> <input type="checkbox"/> Risk assessment and stratification <input type="checkbox"/> Patient education <input type="checkbox"/> Premedication 	<ul style="list-style-type: none"> <input type="checkbox"/> Anesthesia technique <input type="checkbox"/> Opioid selection <input type="checkbox"/> Intravenous acetaminophen <input type="checkbox"/> Nonsteroidal anti-inflammatory drugs <input type="checkbox"/> Regional anesthesia techniques: scalp infiltration, nerve blocks <input type="checkbox"/> Anesthetic adjuvants: dexmedetomidine, ketamine, corticosteroids, lidocaine <input type="checkbox"/> Intra-disciplinary communication via checklist and debrief 	<ul style="list-style-type: none"> <input type="checkbox"/> Opioid selection <input type="checkbox"/> Oral medication transition <input type="checkbox"/> Patient controlled analgesia <input type="checkbox"/> Nonsteroidal anti-inflammatory drugs <input type="checkbox"/> Assessment and medication order set standardization <input type="checkbox"/> Patient centric pain management <input type="checkbox"/> Non-pharmacological pain measures <input type="checkbox"/> Modification of head dressing <input type="checkbox"/> Pain dashboard/feedback to care team

to mitigate pain. Preoperative gabapentin and acetaminophen administration are part of ERAS protocols for non-neurosurgical procedures.^[35]

In patients undergoing craniotomy, preoperative gabapentin administration decreases anesthetic and analgesic consumption up to 48 h after surgery, but it also delays tracheal extubation and increased sedation postoperatively.^[132] The effect appears to be beneficial only when given over an extended period preoperatively and not a single premedication dosage.^[83] Other potential effects include decreased incidence of delirium, possibly due to its opioid-sparing effect,^[73] reduced perioperative anxiety, improved sleep quality,^[115] lowered postoperative nausea and vomiting (PONV),^[83] and attenuated hemodynamic effects from the placement of the pin holder.^[82] The procedure specific analgesic benefit of preoperative administration of acetaminophen is undetermined.

Intraoperative interventions

Standardized anesthesia technique (inhalation *versus* intravenous anesthesia)

A small number of studies, not uniform in design, address anesthetic technique and postcraniotomy pain as well as other outcomes.^[20,77,85] Some studies showed that inhalational anesthesia with sevoflurane is associated with a higher probability of postcraniotomy pain in comparison to intravenous techniques.^[77,85] A Cochrane review of postoperative outcomes did not find differences in the probability of postcraniotomy pain.^[99] Apart from evidence that intravenous techniques reduces postoperatively nausea and vomiting, the authors could not draw definitive conclusions regarding other outcomes.

Intraoperative opioid administration and transitional analgesia

The ultra-short-acting opioid remifentanyl is widely used in neurosurgical anesthesia due to its favorable pharmacokinetic profile, but its use is debated in the context of improving postoperative pain experience. Remifentanyl has a dose-dependent potential to amplify postoperative pain and induce pain sensitization.^[124,138]

This effect is counterbalanced by the potential to shorten neurologic recovery and assessment. Need for early analgesia in recovery doubles when patients receive remifentanyl when compared to other opioids, but it allows for a faster preoperative neurological recovery when appropriate transitional analgesia is used.^[38] Morphine combined with remifentanyl provides for transitional analgesia without compromising the quality of recovery.^[38] Limiting the dose of remifentanyl to less than $0.2 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and combination with other analgesics might be useful to mitigate acute opioid tolerance and opioid-induced hyperalgesia.^[138]

Intravenous acetaminophen

As clinical examination of the awake patient is the mainstay of complication surveillance after craniotomy, medications that provide analgesia without additive sedation are particularly valuable. The administration of acetaminophen is unlikely to cause significant additive sedation and likely to provide additive analgesia. Alone it is not potent enough to control pain after craniotomy^[52,54,134] but an ideal component of multimodal analgesia for acute postcraniotomy pain. Although widely used, the procedure-specific benefit of intraoperative intravenous administration of acetaminophen is not presently established. A retrospective analysis showed that while intraoperative acetaminophen is a safe intervention, no significant differences were found in postoperative pain scores.^[54]

NSAIDs

The intraoperative use of non-selective COX-1/COX-2 inhibitors for the patient undergoing craniotomy is questionable. Due to antiplatelet effects, preoperative use can be linked to intracranial hemorrhage in 1.1% of patients.^[92] Studies provide inconclusive evidence for the safety of drugs such as ketorolac,^[76] demonstrating a higher risk for intracranial hematoma associated with intraoperative use but not in the postoperative setting.^[59] Further, trial studies do not show an increase in complication rates for hematomas, renal failure, or peptic ulcers^[28] following neurosurgery. Though their use remains controversial, emerging studies are now focusing on selective COX-2 inhibitors that appear to be safer with regard to coagulation effects. However, addition of parecoxib does not reduce opioid consumption or alter the incidence or severity of side-effects such as PONV.^[60,137]

Scalp infiltration

Infiltration of the scalp with solutions of local anesthetics is widely performed during neurosurgery. When solutions containing epinephrine are used this technique achieves local vasoconstriction and reduces scalp bleeding. Scalp infiltration also decreases the hemodynamic response to placement of head fixation devices and surgical incision.^[40] Given that pain after craniotomy is thought to be superficial and located to the incision

Table 4: Summary of strategies for the treatment of acute postcraniotomy pain

Treatment	PRO/CON	LOE	References
Codeine	Pro: Historical treatment, widely used Con: Potential respiratory depression and sedation; less effective than morphine; genotype variation	3 RCT	[41,69,106,122,125]
Morphine and long acting opioids	Pro: Widely used, effective, small incremental dosing and/or PCA Con: Respiratory depression and sedation; nausea and vomiting; potential to alter cerebral hemodynamics; quality of recovery	3 RCT	[24,38,122,125]
Tramadol	Pro: Less potential for respiratory depression Con: High risk for nausea and vomiting; potential for inducing seizures	3 RCT	[30,32,43,57,102,125]
PCA	Pro: No major adverse effects; lower pain scores Con: Potential respiratory depression and sedation; prescribing errors; need for staff and patient education	4 RCT	[27,84,87,122]
Intraoperative Acetaminophen	Pro: Analgesia without sedation or respiratory depression; established component of multimodal analgesia; no nausea or vomiting Con: Not adequate alone; benefit not established; requires careful attention to cumulative doses and caution in liver patients	2 RCT	[52,54,134]
NSAIDs Non-selective Cyclooxygenase inhibitors	Pro: Effective; minimal sedation; postoperative use Con: Safety to be established; potential for systemic bleeding; intraop intracranial hemorrhage; does not reduce opioid consumption	1 RCT	[28,76,92]
NSAIDs Selective Cyclooxygenase inhibitors	Pro: Effective; minimal sedation; postoperative use; safer than non-selective agents Con: Benefit not established; caution in cardiac patients	2 RCT	[60,104,137]
Ketamine	Pro: Effective pain relief; improves cerebral perfusion; attenuates hemodynamic response Con: Hallucinations; ill-defined potential to confound neurological assessment	2 RCT	[1,15,45,53,78]
Scalp Infiltration	Pro: Attenuates hemodynamic response; reduces pain in 1 st hour; may decrease long term neuropathic pain Con: Does not reduce need for other medication	6 RCT	[2,7,12,40,71,111]
Scalp Nerve Block	Pro: Attenuates hemodynamic response; superior to scalp infiltration Con: Not adequate alone; benefit not well established	5 RCT	[2,5,36,55,98]
Gabapentin	Pro: Attenuates hemodynamic response; decreases anesthetic and analgesic consumption; anxiolytic; improves sleep quality Con: Delayed tracheal extubation, increase sedation; administration over extended periods	4 RCT	[82,83,115,132]
Nonpharmacological Measures	Pro: No major side effects, tailored to patient preferences Con: Evidence not established	3 RCT	[3,116,135]

NSAIDs: Nonsteroidal anti-inflammatory drugs, RCT: Randomized controlled trial, PCA: Patient controlled analgesia

area,^[11] a potential effect on acute postoperative pain is plausible. Scalp infiltration does not reduce the need for postoperative pain medication.^[2,7,12,71] A review by Hansen *et al.*^[46] demonstrates that scalp infiltration can lead to a significant reduction in the pain scores, but only immediately or shortly after surgery is completed.^[2,13,111,120] Although scalp infiltration does not appear to be effective for the treatment of acute postcraniotomy pain beyond the first hours postoperatively, the benefits may be relevant for the rehabilitation of neurosurgical patients and their quality of life since it may limit the development of persistent pain, particularly neuropathic pain.^[7]

Scalp nerve block

Regional scalp block (SB) is an established technique that involves infiltration of local anesthetic to seven nerves on either side of the head, targeting the major sensory innervation of the scalp.^[16,44] Even though the dura is not accessible to extracranial blockade, it is used as an adjunct to general anesthesia in order to attenuate hemodynamic responses and provide perioperative analgesia.^[2,5,44,89,98] The procedure specific extent and duration of this analgesic benefit is not fully established. Published randomized controlled trial (RCT) on SB are small^[44] and difficult to compare with one another due to the technique's heterogeneous application,

including different choice of local anesthetics and different outcome variables. Nonetheless, it seems that postoperative analgesia provided by SB can last up to 24 h postoperatively and is superior to analgesia provided by scalp infiltration.^[2,5,55,89] Still, some studies have shown that SB was not associated with a more stable intraoperative course, decreased anesthetic requirements, or even decreased postoperative pain.^[36]

The precise assessment of specific side effects and complications for the use of SB is precluded by the small sample sizes of available studies.^[44] As with any type of neural blockade, the risks of local anesthetic toxicity must be considered.^[93] Though relatively safe, care must be taken when performing SB due to the small possibility of transient facial nerve palsy. The SB technique may need to be refined to avoid this complication.^[79]

Dexmedetomidine

Several studies support a role for intraoperative dexmedetomidine in mitigating postcraniotomy pain. Dexmedetomidine has an opioid-sparing effect^[94,119] and provides better control of perioperative mean arterial pressure,^[9] as well as superior analgesia.^[103] Use of dexmedetomidine improved the quality of recovery after major spinal surgery and has been successfully used in non-neurosurgical ERAS protocols.^[8,37]

Ketamine

Ketamine, a phencyclidine derivative with N-methyl-D-aspartate (NMDA) receptor antagonist properties,^[30] provides effective pain relief comparable to opioids.^[15] Its use in patients undergoing craniotomy was initially questioned due to its reported effects on intracranial pressure, seizure threshold, and mentation. Studies have since shown that ketamine does not affect cerebral hemodynamics^[78] and may actually improve cerebral perfusion.^[53] When used in combination with a GABAergic agent, the hallucinatory side effects seem to be blunted.^[53] Use of a subanesthetic dose of ketamine can further attenuate the hemodynamic response to skull-pin placement.^[1] Nonetheless, the lack of available studies and the potential to induce cognitive changes, negative experiences, blurred vision as well as dizziness make it controversial in the neurosurgical population.^[4,45]

Corticosteroids

Corticosteroids, namely dexamethasone, are frequently administered perioperatively in patients undergoing craniotomy in order to mitigate cerebral edema and PONV. The absence of dexamethasone during craniotomy appears to increase postcraniotomy pain.^[85] This finding is consistent with a salutary effect in other surgeries.^[90,110] However, the analgesic benefit of dexamethasone in neurosurgical patients is still only partially defined.^[47,85]

Lidocaine infusion

Perioperative intravenous lidocaine infusion is a component of several enhanced recovery protocols for non-neurosurgical procedures. A review of RCTs revealed improvement in early postoperative pain in patient undergoing abdominal surgery.^[70] Lidocaine administration was shown to improve postoperative analgesia after supratentorial craniotomy.^[95]

Pain management in surgical safety checklist and debrief
The surgical safety checklist includes opportunities to share information about pain risk factors and pain management plans. This can take place before skin incision where the anesthesia team can review patient specific concerns, and at debrief prior to leaving the operating room when the surgeon, the anesthesia professional, and the nurse review the key concerns for recovery and management of the patient.^[156]

Postoperative interventions

Opioid administration

Opioids are the mainstay treatment for early postcraniotomy pain despite a wide array of side effects. The concerns about interference with early postoperative neurologic examination, respiratory depression, nausea, and over sedation are well founded. Small doses, careful titration, and monitoring are emphasized. Most centers administer opioids on an as-needed basis.^[123] Codeine, a weak opioid with limited analgesic effect, is traditionally the opioid of choice in several neurosurgical centers because of a perceived ceiling to respiratory depressant effects and a lower risk of masking of pupillary signs.^[106] Several studies have shown codeine to be inadequate in the management of all postcraniotomy pain.^[69,125] Despite this, codeine continues to be the mainstay of postcraniotomy analgesia in several centers.^[106,125] Morphine analgesia, while superior to other opioids,^[125] has been questioned in the postcraniotomy pain setting because it might influence cerebral circulation and metabolism, with the potential to jeopardize the former.^[24] Hydromorphone is widely used across surgical specialties including neurosurgery for acute pain management. Studies have suggested some advantage of hydromorphone over morphine for analgesia,^[31] though none have specifically addressed this comparison in neurosurgical patients.

Tramadol is less likely to cause respiratory depression compared to other opioids. Despite this potential advantage for neurosurgical patients, tramadol does share the negative side effects of other opioids namely nausea, vomiting, sedation, and drowsiness.^[30] Even though tramadol has been used successfully after craniotomy,^[32,102] its side-effects have limited its use^[57,125] and its efficacy remains lower than that of morphine.^[125] A side effect that adds controversy is the ill-defined risk of tramadol-induced seizures. The incidence in clinical studies, while quite low, is increased by head injury,

stroke, neurologic and psychiatric medication, and cofactors.^[14,43]

Patient-controlled analgesia

Patient-controlled analgesia (PCA) is another option for postcraniotomy pain treatment. Limited studies show it to be subjectively better than nurse-administered analgesia.^[58,84] PCA with either morphine or fentanyl, reduced pain scores without significant differences in nausea, vomiting, or sedation scores.^[27,84,87,122]

Postoperative NSAIDs

Postoperative administration of non-selective COX-1/COX-2 inhibitors, such as ketorolac, in the early postoperative period is an area of controversy.^[104] Some centers introduce them in a selective criteria based fashion, e.g. in uncomplicated cases with no clotting issues or after 6, 12, or 24 h.^[65] Several studies have shown no adverse effect of postoperative administration.^[59]

Consistent postoperative pain management

Part of ERAS protocols is standardization of postoperative pain orders, pain assessments, side effect appraisals, and early switch to oral medication. The goal is to provide consistent analgesia and minimize breakthrough pain.^[128]

Patient-centric pain management

Patient-centric pain management may reduce the likelihood of over treatment with opioids. Prior studies showed that patients may consider pain tolerable and not desire treatment despite the intensity of pain.^[26,39] Descriptors of tolerable pain and pain documentation help to empower patients in the management of their pain after neurosurgery.^[133]

Nonpharmacological pain reduction techniques

Nonpharmacologic therapies for postsurgical pain include the application of heat and cold, massage therapy, aromatherapy, guided imagery, music therapy, biofeedback, hypnosis, and acupuncture. Live music therapy using patient preferred music has shown to decrease anxiety and stress, but not pain or analgesic requirements, after elective craniotomy.^[135] Periorbital cryotherapy was shown to decrease eyelid edema and ecchymosis, but not postcraniotomy pain scores.^[116] Electroacupuncture decreased pain scores in the first 6 h after supratentorial craniotomy.^[3] The potential value of other nonpharmacological strategies to mitigate pain mentioned above, as well as patient education and pain management planning have not been studied in patients undergoing craniotomy.

Modification of head dressings

Patients complain of discomfort related to the tightness of the circumferential head dressings used to reduce the risk of subgaleal fluid collection. Formal analysis or review of the type of dressing and its relationship to pain experience has not yet been performed. Skin necrosis is

reported as a complication of a head dressing wrapped too tightly.^[118]

Feedback to care team using pain dashboard

Dashboards can drive compliance with patient care protocols.^[81,133] Pain outcome internal benchmarking has been associated with improved pain outcomes after non-neurosurgical procedures.^[10]

SUMMARY AND CONCLUSIONS

The study of postcraniotomy pain is challenging because of several confounding variables. These include the use of different intraoperative anesthetics/opioids, lack of standardized postoperative pain management protocols, subjectivity of pain assessment techniques, and the patients' neurological status.^[127] Several promising studies have tried to determine better ways of coping with this issue, despite the fact that experts and recent surveys increasingly emphasize that postcraniotomy pain continues to be poorly managed, crudely understood, and undertreated. We identified multiple studies that support an opportunity for improving pain management. Standardized care management protocols are one approach to improving these outcomes. The information on the potential benefits in patients undergoing neurosurgery is limited to a single quality improvement trial. Results from this study demonstrated that the implementation of a standardized analgesia protocol for neurosurgery resulted in a significant reduction in early postoperative pain scores after spine surgery but not craniotomy surgery.^[130]

This current review outlines the options pertinent to the perioperative management of craniotomy pain. Information on perioperative pain management options is widely available from research studies, quality improvement trials, and enhanced recovery protocols for non-neurosurgical procedures. Examination of procedure specific foundation for each care management option reveals a paucity of randomized controlled and data driven studies,^[87] on which to base definitive best practice standards.^[51] Pending additional studies, perioperative pain management care pathways are promising practices with acceptable risk.

The potential benefits of standardized perioperative pain management pathways include simplification, decreased variation, and reduced possibility of error as well as improved outcomes. Creating a pathway that requires consensus between nurses, physicians, and allied professionals also provides an opportunity for the entire perioperative care team to review local pain management processes and the objective evidence supporting each care management intervention.

Pain management begins in the preoperative period with risk assessment, patient education, and administration of oral medications, when appropriate. While the

modification of operative techniques might be useful in pain reduction, anesthetic management, and the use of different analgesic techniques, such as regional blocks, adjuvants, or alpha-2 adrenergic agonists, are potentially important areas of interest. Opioids are still the mainstay treatment for postcraniotomy pain, but several other interventions have the potential to improve outcomes. Multimodal analgesia, nonpharmacological techniques, standardized pain management protocols, and empowering the patient in the management of their pain are all possible avenues for success. Future research on mechanisms, predictors, treatments, and pain management pathways will help define the combinations of interventions that optimize pain outcomes.

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Conflicts of interest

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