



# A Contemporary Perspective on the Management of Post-Craniotomy Headache and Pain

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## Abstract

**Purpose of Review** This article discusses the etiology and management of post-craniotomy headache and pain. A review of available as well as investigatory treatment modalities is offered, followed by suggestions for optimal management of post-craniotomy headache.

**Recent Findings** There is a dearth of evidence-based practice regarding the differential diagnosis, natural history, and management of post-craniotomy headache. The etiology of post-craniotomy headache is typically multifactorial, with patients' medical history, type of craniotomy, and perioperative management all playing a role. Post-craniotomy headaches are often undertreated, yet available evidence supports a multimodal approach for both prophylaxis and management. Many therapeutic techniques that aim to treat or prevent post-craniotomy headache require more robust validation than clinical evidence currently imparts. Pre- and intraoperative locoregional anesthesia should be the mainstay of prophylaxis; the role of opiates co-administered with analgesics, corticosteroids, and antiepileptic therapy in the acute perioperative phase is of paramount importance. Treatment of chronic PCH is less well-defined but should involve trials of analgesic, antineuropathic, and antiepileptic medications before enlisting experimental treatments. Comorbid psychiatric, musculoskeletal, or seizure disorders should be managed distinctly from post-craniotomy headaches. In patients failing all extant therapies, experimental approaches should be considered. These include subanesthetic ketamine infusion or surgical site injection with local anesthetics, corticosteroids, or botulinum toxin.

**Summary** Post-craniotomy headache is a complex phenomenon with many underutilized treatment options available, and many more under investigation. Nonetheless, further research is required to differentiate the efficacy of contemporary treatment strategies and to elucidate the applicability of novel therapies.

**Keywords** Headache · Craniotomy · Postoperative pain · Chronic headache · Chronic pain · Neurosurgery

## Introduction

Craniotomy is one of the most common neurosurgical procedures and is performed for a variety of indications including treatment of intracranial tumors, aneurysm clipping, and

epilepsy surgery. However, post-craniotomy care, specifically with respect to pain and headache, continues to be a topic of contention in the neurosurgical world.

De Benedettis et al. conducted the first documented study to assess postoperative pain in neurosurgery [1] and found that approximately 60% of patients experience moderate to severe pain [1]. Since then, numerous other studies have corroborated their findings, but no consensus has been reached on the optimal way to treat post-craniotomy headache (PCH). In most surgeries below the neck, the postop pain algorithm is fairly well-defined: multimodal analgesia with opioids and NSAIDs [2•]. In the management of a neurosurgical patient, attention must be paid to the neurologic examination, and opioids can confound the examination considerably by causing miosis, sedation, and concealing signs of intracranial emergencies [2•]. For this reason, surgeons are hesitant to use the most potent tool, opioids, in the fight against patient's pain. Further

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muddying the picture is the perception that brain surgery is less painful than other surgeries. Reasons for this belief include fewer pain receptors in the dura, pain insensitivity of the brain, reduced pain fiber density along incision lines, and development of autoanalgesia [3•]. A more recent study by Mordhorst et al. [2•] found that 55% of patients experienced moderate to severe pain in the initial 24-h post craniotomy [2•].

The issue of PCH is an important one for a number of reasons. Among patients with PCH, 29–60% report that the headache interferes with daily activities, such as sports (25%), work (19–38%), and social activities (8%). In 15% of the cases, PCH has a negative impact on mood, and in 22%, the pain is incapacitating [4]. The issue is an understudied one, and in this review, we aim to summarize the existing literature. We briefly elaborate on the anatomy and pathophysiology associated with postoperative pain and headache in the neurosurgical patient, then explain current options for treatment of acute and chronic PCH, before discussing at the ongoing research and future directions.

## Classifications

The International Headache Society published the International Classification of Headache Disorders (ICHD-3) in 2013, an update to their diagnostic criteria for different headaches previously published in 2004. In it, they laid out the diagnostic guidelines for both acute PCH and persistent, or chronic, PCH. The criteria are thus [3•]:

### Acute Headache Attributed to Craniotomy

#### Description:

Headache of less than 3 months' duration caused by surgical craniotomy.

#### Diagnostic criteria:

1. Any headache fulfilling criteria C and D
2. Surgical craniotomy has been performed
3. Headache is reported to have developed within 7 days after one of the following:
  - (a) The craniotomy
  - (b) Regaining of consciousness following the craniotomy
  - (c) Discontinuation of medication(s) impairing ability to sense or report headache following the craniotomy
4. Either of the following:
  - (a) Headache has resolved within 3 months after its onset

- (b) Headache has not yet resolved but 3 months have not yet passed since its onset
5. Not better accounted for by another ICHD-3 diagnosis.

### Persistent Headache Attributed to Craniotomy

#### Description:

Headache of more than 3 months' duration caused by surgical craniotomy.

#### Diagnostic criteria:

1. Any headache fulfilling criteria C and D
2. Surgical craniotomy has been performed
3. Headache is reported to have developed within 7 days after one of the following:
  - (a) The craniotomy
  - (b) Regaining of consciousness following the craniotomy
  - (c) Discontinuation of medication(s) impairing ability to sense or report headache following the craniotomy
4. Headache persists for > 3 months after its onset
5. Not better accounted for by another ICHD-3 diagnosis.

## Anatomy and Pathophysiology

### Anatomy

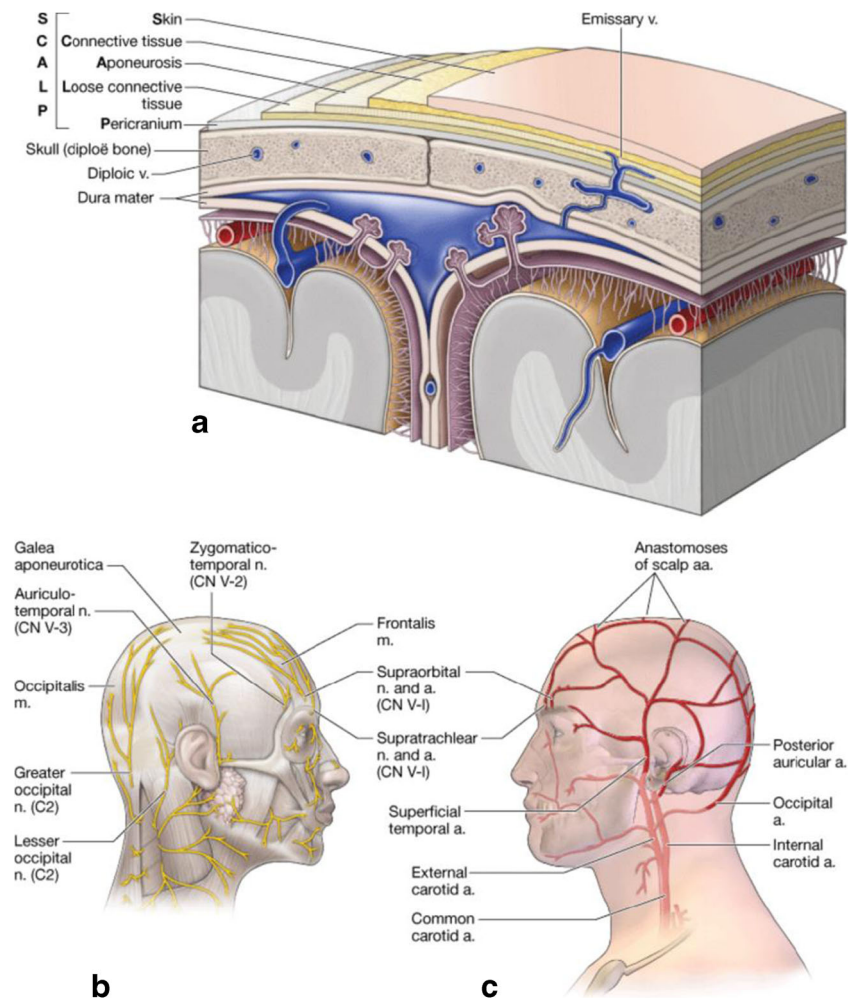
The skull is made up of both the facial skeleton and the calvarium. The base of the skull is exposed once the calvarium is removed. It is divided into the anterior, middle, and posterior cranial fossae. On the underside, a number of foramina become apparent through which the brain stem, cranial nerves, and a number of blood vessels traverse.

The inside of the skull is comprised of a fibrous membrane, the endocranium, which makes up the outer part of the dura. This becomes continuous with the periosteum on the outer surface of the skull and becomes the pericranium.

The two muscles of the epicranium are the occipitofrontalis and temperoparietalis. The galea aponeurotica, in concert with occipitofrontalis, makes up a continuous fibromuscular sheet covering the entire cranium. In total, the scalp is made up of five layers: skin, subcutaneous tissue, epicranial aponeurosis, subaponeurotic areolar tissue, and the pericranium (Fig. 1).

Deep to the scalp (post-craniotomy) are the meninges: the dura mater, arachnoid mater, and pia mater. The cerebral dura is comprised of an internal periosteal layer and a supporting membrane for the brain. The innermost pia is adherent to the parenchyma.

**Fig. 1 a** Coronal section of the head. Cutaneous innervation (**b**) and arterial supply (**c**) to the scalp. Used with permission from McGraw-Hill Education. Source: Morton DA, Foreman KB, Albertine KH: *The Big Picture: Gross Anatomy*. www.accessmedicine.com. Copyright © The McGraw-Hill Companies, Inc. All rights reserved



Innervation of the scalp and dura is multifold:

- Trigeminal nerve, including its ganglion, the three principal divisions and their branches
- Upper three cervical nerves
- Cervical sympathetic trunk
- Minor branches from the vagus nerve
- Minor branches from the hypoglossal nerve
- Minor branches from the facial nerve
- Minor branches from the glossopharyngeal nerve

Craniotomy can be approached supratentorially or infratentorially, with differing indications for the various approaches.

### Pathophysiology

The pain patients typically describe post-craniotomy is superficial [1], which is to be expected with the paucity of

pain receptors in the actual brain parenchyma. Thus, post-craniotomy pain must originate from the superficial structures, namely, the soft tissues and pericranial musculature. This theory is further substantiated by anecdotal evidence that subtemporal and suboccipital approaches are associated with the highest incidence of pain, likely due to stress placed on the splenius capitis, temporal, and cervicis muscle tissues during surgery [2•]. The pain is nociceptive in quality and induced by the incision and reflection of the pericranial muscles [1, 5].

PCH has a slightly different pathogenesis. It is likely multifactorial, with only a few of the possible causes listed here. One theory suggests that pericranial muscular adherence to the dura may lead to PCH [4]. Patients undergoing suboccipital craniectomy have a higher incidence of headaches than patients undergoing craniotomy [4, 5], and adherence between the dura and cervical musculature has been proven histopathologically in a patient suffering from chronic postsurgical headache [4]. Another leading theory argues that aseptic

meningitis caused by bone drilling during surgery may lead to PCH [4]. Finally, some evidence points to neuromas or nerve entrapment in the surgical scars being responsible for headaches [6].

It is important to note that the pathogenesis of PCH likely involves more than simple anatomical insults as suggested above. Higher cortical and subcortical systems are likely at play, as prolonged changes in central neural function induced by surgery may contribute to postoperative pain and headache [1]. These complex mechanisms, mainly sensitization and wind-up, are not completely understood and are beyond the scope of this review, but any discussion of PCH would be incomplete without mentioning the role of neurotransmitters and these neurological phenomena that may be associated with PCH.

The binary classification of PCH proposed by the ICHD-3 beta (elaborated above) does not reflect the spectrum of pathological pain associated with craniotomy. Acute pain and headache may persist to become chronic pain and headache, or the latter may occur long after the procedure. We discuss a preemptive, perioperative, and chronic approach to management of the PCH.

## Preoperative Considerations

Preemptive analgesia is an important strategy used to blunt hemodynamic responses to intraoperative pain, [7] to prevent acute postoperative pain, and to prevent hypersensitization causing persistent pain and headache [2•, 3•, 5]. Preoperative analgesia by infiltration of wound margins or by scalp block can prevent hypersensitization by blocking peripheral neural response to local tissue damage and inflammation and by preventing transmission of pain signals that would lead to central hypersensitivity, thus reducing the likelihood of chronic PCH developing [2•, 3•].

Preoperative analgesia with surgical site infiltration has been shown to reduce postoperative pain [2•] and postoperative opiate requirements [2•]. Similar results have been seen with preoperative scalp block<sup>7X</sup>; scalp block has also been noted to delay the first request for postoperative analgesics and decrease the frequency of breakthrough pain thereafter [3•]. Studies using different combinations of ropivacaine, bupivacaine, and lidocaine for both site infiltration and scalp block have demonstrated persistence of analgesia ranging from 2 to 48 h after administration [2•, 3•, 5]. Differential efficacy of the various approaches to scalp innervation blockade requires further elucidation, and novel techniques such as maxillary nerve block (with the intent of causing total ipsilateral trigeminal nerve block) should be compared to standard modalities as well [7].

Pre-craniotomy administration of antiepileptic drugs, as part of an existing regimen or as prophylaxis for post-

craniotomy seizures, is common and advisable in circumstances where the risk for post-craniotomy seizures is high and intraoperative seizure focus mapping is not planned. Beyond the immediate pragmatic implications, anticonvulsants can also play a role in preemptive management of PCH. Gabapentin has been shown to decrease postoperative pain and opioid requirements [2•] and is well known for its role in treating chronic and neuropathic pain. It has been shown to have equal efficacy to phenytoin for seizure prophylaxis in patients undergoing supratentorial tumor resection while significantly reducing postoperative nausea, vomiting, pain, and opiate consumption [2•, 3•].

Like antiepileptics, corticosteroids are also commonly administered preoperatively. By reducing edema and inflammation, corticosteroids may act prophylactically against PCH to decrease tension against injured dura or by reducing the severity of aseptic meningitis. They also may increase patients' tolerance to opiates' side effects [2•, 3•, 5, 8].

NMDA receptor antagonists' role as preemptive analgesics has yet to be thoroughly explored, but there is some evidence that preincisional dextromethorphan administered with or without ketamine acts to reduce postoperative pain and opiate requirements, hypothetically by preventing central sensitization to painful stimuli [2•, 3•]. Although ketamine's effects on ICP are controversial, it has dual potential as a preemptive analgesic and IV induction agent.

## Intraoperative Considerations

The operative approach affects patients' risk for PCH and is a potential target of modification. Using dura plastic, replacing the bone flap, and taking care to keep bone debris away from the surgical site are potentially prophylactic measures against increased muscle tension or aseptic meningitis in the postoperative phase. Incision of the temporal muscle with a monopolar device or scraping muscle fibers off the temporal bone are two ways the temporalis muscle can be damaged [8]. There is evidence that temporomandibular disorders following craniotomy are an etiology of chronic headache [9] so using a scalpel for incision of the temporalis and carefully repairing affected musculature could prevent the tissue damage that leads to acute surgical site pain and chronic PCH [2•, 3•, 5, 8, 9].

Remifentanyl use for intraoperative anesthesia is another potential factor in the development of PCH as its withdrawal is associated with hyperalgesia [2•]. Remifentanyl use is also associated with increased postoperative analgesic requirements [2•]. Sufentanil or other opiates may be appropriate substitutes while avoiding the risk of acute or chronic hyperalgesia.

## Transitional Anesthesia

When transitioning from surgical anesthesia, a multimodal approach can be taken to minimize the onset of acute pain and PCH. Local anesthesia should be brought to the maximum allowable dose by wound infiltration or scalp block [3•]. The intraoperative short-acting opiate should be exchanged for a longer acting drug-like morphine, which can reduce subsequent morphine requirements [2•]. Co-administration of dexmedetomidine, an alpha 2 adrenergic agonist, can combat postoperative distress and agitation while potentially reducing opiate requirements by as much as 60% [3•].

## Acute Postop Pain and Headache Management

A variety of pharmacologic approaches is available for managing surgical site pain and PCH. There is considerable apprehension towards opiate use, stemming from side effects that may confound the neurologic exam or directly impede recovery. Nonetheless, parenteral opiate administration is the mainstay of therapy [3•]. Morphine is the most commonly used opiate to treat PCH [3•]; it is more effective than codeine [2•], which is a prodrug of morphine with variable rates of metabolism in different patients but with a similar side effect profile to morphine [2•, 3•]. Synthetic opioids may be equally suitable compared to morphine and can be selected based on their duration (regarding the frequency of neuro exams) or for transitioning from IV to PO regimens. Notably, sufentanil infusion was shown to be equally efficacious compared to morphine in terms of pain control and hemodynamic stability, while reducing the incidence of nausea and vomiting [2•].

Abundant evidence supports the use of IV PCA over PRN analgesia in many settings [2•], and treating PCH is not an exception. Morphine administered by IV PCA is associated with reduced pain scores and decreased incidence of side effects, while increasing patient satisfaction [3•]. IV fentanyl PCA has been shown to provide superior pain reduction compared to PRN therapy without significantly affecting respiratory function or patient alertness and without impacting providers' ability to perform neuro exams [2•]. Use of fentanyl as opposed to morphine when administered by PCA is considered more prudent by some because its shorter duration preserves patient alertness, and because patient competence is key to proper use of PCA analgesia [3•]. PCA analgesia may also reduce opiate requirements, as patients commonly use less than half of their allotted medication [2•].

In patients without risk for developing prolonged QTc, methadone, a drug possessing opiate agonist and NMDA receptor antagonist activity, is an understudied but potentially viable option for both acute pain management and prevention of sensitization leading to chronic PCH [2•]. Its longer

duration of action and utility in preventing opiate abuse make it a potential candidate for step-down regimens.

Adjunct non-opioid analgesics are an important part of pain management and reduce the use of opioids. Acetaminophen, while inadequate for pain relief by itself [2•], is an excellent addition to opioid regimens. It does not have significant side effects, nor does it alter the side effect profile of opioids. Acetaminophen improves pain scores and reduces opiate requirements significantly [3•]. There is support for co-administration of various other analgesics in the acute setting. Tramadol has been shown to improve pain scores in post-craniotomy patients, decrease analgesic requirements, and reduce length of stay and overall cost associated with treatment [2•]. However, it is also associated with significant side effects such as nausea, vomiting, and dizziness [2•] which may be worse than the nausea or vomiting caused by morphine [2•]. Tramadol PCA was shown to be inferior to morphine PCA for both analgesia and patient satisfaction [2•]. Tramadol has also been associated with seizures when administered as an IV bolus [3•].

NSAIDs are approached with caution in the neurosurgical setting due to the risk of ICH secondary to impaired platelet aggregation and are a major risk factor for post-craniotomy hemorrhage [2•] and postoperative renal failure [5]. Indomethacin is reported to reduce cerebral blood flow due to vasoconstriction [3•]. Despite their risks, NSAIDs are routinely prescribed by neurosurgeons in the UK [2•] and their utility for management of headache and reduction of postoperative pain and opiate requirements in many surgical settings is well established [2•]. Hoping to circumvent the pitfalls of NSAID use, studies of COX-2 inhibitors showed reduction of post-craniotomy pain without increased risk of hemorrhage [2•], shortened hospitalization time and increased patient satisfaction [3•], and reduction of opiate consumption [2•]. However, the increased risk of thrombosis and cardiovascular adverse events has undermined appreciation for COX-2 inhibitors as a viable option [2•, 3•].

Finally, in the acute setting, cryotherapy to wounds and the periorbital areas using ice packs should be considered as a cheap and non-invasive way to reduce inflammation, edema, and pain [3•].

## Chronic PCH

The approach to chronic PCH should be specific to the symptomatic manifestations that patients report [4]. Various types of headaches have been reported after craniotomy, and treatments typically align with the suspected etiology. Regardless of the cause of headache, comorbid psychiatric illness or cervical spine disease are potential barriers to treatment and should be addressed. With regard to headaches, low impact medications like NSAIDs and acetaminophen should be tried

as first line options [3•, 5], with the caveat that medication withdrawal headaches may occur if first line treatments are stopped abruptly [4, 5].

After the first line treatments fail, chronic PCH have been commonly treated with opiates and other analgesics. Tricyclic antidepressants are used as adjuncts in many practices [5]. Case reports indicate PCH can be aborted with sumatriptan [4]. There is evidence demonstrating that verapamil, sodium valproate [4], and other antiepileptics like lamotrigine, topiramate, carbamazepine, and tiagabine may have a role in treating PCH when the presentation of pain is mainly neuropathic or involvement of the trigeminal nerve is suspected [3•, 5]. Hyperalgesia or allodynia should be singled out as indications for the use of gabapentin [3•, 5]. Considering that the incidence of seizures both before and after craniotomy is high, the efficacy of antiepileptic drugs in treating PCH may in part be due to secondary prevention of seizure associated headaches [5].

Pain over surgical scars may be an indication for locoregional therapy. Topical analgesics, topical steroids, topical NSAIDs, and cryotherapy with ice packs should be employed before more invasive treatments. A study of four patients showed that injection of surgical scars with local anesthetic and corticosteroids was an effective treatment modality, theoretically because neuromas or nerve entrapment within the scars was the etiology of these patients' headaches [6]. Two case studies in a total of seven patients show that injection of botox either into peri-incisional areas or directly into the temporalis muscle dramatically reduced headaches for extended periods, with remission lasting months to years after treatment [10, 11]. While the analgesic impact of peri-incisional botox injection supports the hypothesis that structural lesions near surgical sites may cause persistent PCH, the efficacy of temporalis muscle injection points to temporomandibular dysfunction and orofacial pain as the culprit. Prevention of persistent PCH secondary to temporomandibular dysfunction may be achieved by screening for muscular abnormalities with electromyography [3•] and addressing the issue early in the postoperative course.

Future directions for research include further validation of extant methodology as well as investigation of novel techniques. There are other modalities used to address chronic pain that have yet to be assessed in PCH. SNRI's have not been studied for the treatment of PCH, but there is evidence that duloxetine can be used to treat neuropathic pain and to prevent tension headaches [12]. The benefit seen with tramadol in the perioperative setting supports the potential use of SNRIs for treating chronic PCH.

The use of ketamine for the treatment of persistent PCH has not been documented, but subanesthetic infusions of ketamine administered over the course of several days have shown tremendous efficacy in acute management of several types of chronic treatment-resistant headache disorders. Statistically

significant-sustained benefit from these treatments is still under investigation [13]. Other chronic pain disorders such as complex regional pain syndrome and fibromyalgia have also seen benefit from subanesthetic continuous ketamine infusion [13]. There is also evidence that when combined with magnesium, subanesthetic ketamine infusion is effective for the treatment of cluster headaches [14]. It stands to reason that patients with persistent treatment-resistant PCH would be excellent candidates for the study of continuous subanesthetic ketamine infusions.

Cannabis-derived products are an overlooked modality for the treatment of PCH. With the political and medical communities becoming more accepting of the use of cannabis for medical purposes, it may be reasonable to turn to cannabinoids as potential treatment for PCH. There are no randomized clinical trials or placebo-controlled studies of cannabis for the treatment of chronic headache disorders. However, there are abundant case reports indicating that cannabis can be used as prophylaxis or an abortive agent, or for alleviation of symptoms, in treating a variety of types of chronic headaches such as migraines, tension headaches, pseudotumor cerebri, and MS-associated trigeminal neuralgia. Synthetic cannabinoids are similarly supported by case reports for the treatment of chronic headaches, including cluster headaches and medication-overuse headaches [15]. The non-psychoactive cannabinoid CBD may deserve particular attention. It has been shown to treat a variety of childhood epilepsy syndromes in case reports, and clinical studies have shown it is effective for reduction of seizure activity in adults [16]. Given the potential for cannabis products to treat headaches and the current use of antiepileptic drugs to treat PCH, it seems that CBD is a logical candidate for studying the utility of cannabinoids in the post-craniotomy patient.

## Conclusion

Post-craniotomy headache is a complex condition that has multiple etiologies, commonly occurs acutely, and can persist or recur chronically. These headaches can be debilitating for patients, yet are often undertreated. The approach to post-craniotomy headaches should start with preventive efforts in the perioperative setting, such as the concomitant administration of local anesthesia, corticosteroids, antiepileptics, and NMDA antagonists. Intraoperatively, modification of surgical technique and judicious selection of opiates can also reduce the incidence of post-craniotomy headache. In the acute postoperative phase, a multimodal and active approach to analgesia should be employed. If chronic headache develops, proper diagnosis (to the exclusion of comorbid psychiatric or musculoskeletal disorders) is imperative. There are several tiers of non-opiate treatment options to exhaust before considering experimental therapies. In general, post-craniotomy headache

is understudied and there are few strong clinical studies evaluating the relative efficacies of different treatment options. Our stance and recommendations are based on the best available evidence, but further research for both existing and novel treatments is necessary to truly define the best possible way to spare patients from the pain and headaches that follow craniotomy.

### Compliance with Ethical Standards

**Conflicts of Interest** The authors declare that they have no conflicts of interest.

**Human and Animal Rights** This article does not contain any studies with human or animal subjects performed by any of the authors.

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