




Post-craniotomy Pain: An Update

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Abstract

Approximately two-thirds of patients experience moderate to severe intensity pain following craniotomy. It is often undertreated due to fear of unfavorable side effects of commonly used analgesic drugs. The objectives of this review are to discuss the various aspects of acute and chronic post-craniotomy pain including its incidence, pathophysiology, diagnostic criteria, preventive strategies, and management in adult patients. The data have been consolidated based on our literature search from 1978 to 2021 using various databases including Google Scholar, Medline, and PubMed Central. We conclude that one must act at the earliest using various treatment modalities for post-craniotomy pain management.

Keywords

- ▶ acute post-craniotomy pain
- ▶ chronic post-craniotomy pain
- ▶ scalp bloc

Introduction

Post-craniotomy pain is significant but underdiagnosed and undertreated complication for neurosurgical patients. It affects patient satisfaction, and their day-to-day activities and increases morbidity. This article describes the incidence, pathophysiology, risk factors, prevention, and management of acute and chronic post-craniotomy pain in adult neurosurgical patients as per the recent guidelines. The data were searched from 1978 to 2021 using various search engines including Google Scholar, Medline, and PubMed Central while writing this review using “acute post craniotomy pain, chronic post craniotomy pain, risk factors of post craniotomy headache, management of post craniotomy pain” as keywords. After inserting these keywords, we got 81 hits. We excluded articles with only abstracts and protocol publications and articles other than in the English language. We included 34 RCTs, 22 observational studies, and 3 case reports (for novel techniques only) in this review.

Acute post-craniotomy Pain

Acute post-craniotomy pain is defined as a headache of lesser than 3 months in duration that is caused due to surgical craniotomy.¹ De Benedittis et al conducted a landmark study in 1996 to assess the incidence, magnitude as well as the duration of acute pain in 37 neurosurgical patients who had undergone various types of neurosurgical procedures. They found that post-craniotomy pain was much more common (60%) than the general assumption and the intensity was moderate to severe in two-thirds of patients. Pain occurred most frequently within the first 48 hours postoperatively; however, a significant number of patients suffered from pain for longer periods.² Peon et al in their study of 40 neurosurgical patients found that 85% of patients reported headaches in the preoperative period. This was increased to 93% of patients in the postoperative period. The peak pain was noticed on the second postoperative day, wherein 32% of patients suffered severe pain and 27% had moderate pain. They also observed that patients did not report any severe pain after the eighth postoperative day.³

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A recent study of 256 patients undergoing elective craniotomies found that 87% of patients had pain on the first postoperative day. Among these, 32% had mild pain, 44% had moderate pain, and 11% had severe pain.⁴

The diagnostic criteria of acute post-craniotomy pain include a headache that develops within 7 days after one of the following events, including craniotomy, regaining of consciousness after craniotomy, and discontinuation of medications that impair the ability to sense. It usually resolves within 3 months after its onset and should not be accounted for by another *International Classification of Headache Disorders* (ICHD-3) diagnosis.¹

Pathophysiology

Acute post-craniotomy pain is mostly superficial in nature and is somatic in origin arising from soft tissues and pericranial muscles. The highest incidence of pain has been found to be associated with subtemporal and suboccipital pathways and is nociceptive in nature. It has been found to be induced by surgical incision and reflection of major muscles such as temporalis, splenius capitis, and cervicis. Numerous causes of headache after craniotomy include cervicogenic headache (secondary to positioning during surgery and extensive local tissue dissection, hydrocephalus, headache from cerebrospinal

fluid [CSF] leak, intracranial hemorrhage, space-occupying lesions [blood/edema/residual tumor]), and infections.² The pain can be pounding or pulsating type as seen in a tension headache or might be a more constant or continuous type of pain.⁵

The factors responsible for post-craniotomy pain can be divided into various preoperative and intraoperative factors and are summarized in ► **Table 1**.^{4,6–24}

Assessment of Post-craniotomy Pain

The first step in the management of pain or headache is the assessment of pain. It can be assessed using various scales and questionnaires.

Acute pain is usually measured by the Numeric Rating Scale (NRS) and Visual Analog Scale (VAS), while chronic pain is measured by McGill Pain Questionnaire and Brief Pain Inventory.²⁵ The NRS is a discrete score ranging from 0 to 10, where 0 means no pain and 10 means the worst pain the patient has ever felt. VAS scale represents the structure with orientation to pain on a horizontal scale with the worst pain represented on the left and no pain represented on right. McGill Pain Questionnaire measures sensory, affective, and total pain index. The Brief Pain Inventory encompasses seven aspects of life with which pain interferes, including general

Table 1 Factors affecting post-craniotomy pain

Preoperative	
Age	Greater incidence in young patients ⁴ Reduction in VAS score by -0.18 U with every year of age ⁵
Gender	Greater incidence and severity in females ⁶
Preoperative Headache	Greater incidence and severity in patients with pre-existing pain ⁷
Psychological Factors	Higher pain intensity in patients with anxiety symptoms ⁴
Intraoperative	
Tumor characteristics	
Type of tumors	Higher incidence in patients with astrocytomas and metastatic brain tumors ⁸
Size of tumors	Higher incidence of chronic PCH in patients with small size of tumor ⁹
Location of tumors	Higher incidence in intraventricular and infratentorial space tumors ⁸
Site of surgery	Higher pain incidence and severity in infratentorial procedures as compared with supratentorial procedures. ^{10,11}
Type of surgery	
Craniotomy vs. Craniectomy	Lower pain intensity in craniotomy as compared with craniectomy ¹² .
Cranioplasty vs. no Cranioplasty	Lower pain scores in patients who underwent cranioplasty after craniotomy as compared with no cranioplasty-associated craniotomy ¹³ .
Extent of muscle resection	More pain with larger resection ¹⁴
Surgical approach	Less persistent pain in translabyrinthine approach vs suboccipital or retrosigmoid approach ^{10,15–19}
Removal of bone dust	Lower incidence of pain ¹⁹
Direct closure of dura vs. duroplasty	100% incidence of pain in patients with direct closure of dura as compared with 0% in the duroplasty group ²⁰ .
Type of anesthesia	Lower pain scores in TIVA as compared with inhalational agents ²¹
Role of steroids	Lesser pain in patients on preoperative steroids ^{21–24}

Abbreviations: PCH, post craniotomy headache; TIVA, total intravenous analgesia; VAS, visual analogue scale.

activity, normal work, walking, interpersonal relationship, mood, enjoyment of life, and sleep.

Management of Acute Post-craniotomy Pain

The management of acute post-craniotomy pain consists of preventive strategies aimed at decreasing the occurrence of post-craniotomy pain and treatment modalities for the management of pain, once it occurs. Various preventive and treatment modalities are described as follows.

Preventive Strategies

Modification of Surgical Techniques

Tight dura or scalp wound closure produces a constant strain on the respective structures that may stimulate the corresponding nerve and may be one of the potential causes of excessive pain. A few modifications of the surgical techniques have been described in the literature. These include preferring craniotomy (replacing the bone flap) over craniectomy (no replacement of the bone flap), use of methyl methacrylate between the dura and cervical muscles for wound closure, use of extradural abdominal fat graft for closure during retrosigmoid craniotomy instead of standard wound closure techniques, and duraplasty is preferred instead of direct closure of dura.^{15,18,22}

Pre-emptive Analgesia

This includes the use of scalp infiltration, scalp block, and pre-emptive non-steroidal anti-inflammatory drugs (NSAIDs).

Scalp infiltration involves infiltration of the surgical site with a local anesthetic agent. Various studies have been conducted using anesthetic agents such as bupivacaine (0.25%, 0.375%, and 0.5%) and ropivacaine (0.75%). Patients in the study group have been found to have decreased VAS scores and decreased requirements for rescue analgesic agents.^{24,26–29}

The scalp and dura are richly innervated by the trigeminal nerve and its branches, the first three cervical nerves and its branches, the cervical sympathetic trunk and minor branches arising from the vagus nerve, hypoglossal nerve, facial nerve, and glossopharyngeal nerve. These nerves are blocked by either a ring block from nasion to external occipital protuberance or by blocking the individual nerves. Various commonly blocked nerves during scalp block include the supraorbital nerve, supratrochlear nerve zygomaticotemporal nerve, auriculotemporal nerve, lesser occipital nerve, greater occipital nerve, and greater auricular nerve.³⁰

The scalp block may be given either before the start of surgery (pre-emptively) or at the end of the surgery. History of prior craniotomies may affect the efficacy of scalp block as the scars may inhibit the spread of the local anesthetic, resulting in an ineffective or incomplete block. Any skull defects must be ruled out to avoid injury to the underlying parenchyma. Strict aseptic precautions must be followed. The total safe dose of a local anesthetic agent must be calculated based on the weight of the patient. The amount to be injected at each site is dependent on the local anesthetic agent, its concentration as

well as if an additive such as epinephrine has been used or not. The complications associated with scalp nerve block are intravascular injection, intraneural injection (higher chances during supraorbital nerve block because of its anatomical position), inadvertent injection in the superficial temporal artery, temporomandibular joint, and the facial nerve (auriculotemporal nerve block), and injection in subarachnoid space.^{31,32}

Evidence Showing Efficacy of Scalp Block

A meta-analysis by Wardhana et al comprising 10 studies and 551 patients found a statistically significant reduction in the mean pain intensity in the scalp block group as compared with the no scalp block group at a very early and early 24-hour period.³³ Opioid requirements were also decreased in the first 24-hour postoperative period. They found scalp block to be useful at less than 6 hours post-craniotomy period with very-low quality evidence.

In another meta-analysis by Guilfoyle et al, comprising seven RCTs and 320 patients, preoperative scalp block was given in three studies and postoperative scalp block after the closure of the wound in the other four studies.³⁴ There was a pooled reduction in pain score at 1 hour postoperatively. There was a significant decrease in pain scores at 2, 4, and 6 to 8 hours postoperative period, wherein scalp block was administered preoperatively and a significant decrease in pain scores at 2, 4, 6 to 8, and 12 hours in patients to whom scalp block was administered postoperatively. Total opioid requirements in the first 24 hours were also found to decrease although with significant heterogeneity between the studies.

Role of Pre-emptive NSAIDs

Post-craniotomy pain is nociceptive in nature; hence, the preoperative administration of NSAIDs might decrease the local inflammation and its resultant sensitization and pain windup occurring during craniotomy as seen in one study. Because the analgesic benefit persisted for 5 days postoperatively, which is much more than the duration of action of the analgesic drug; hence, efficacious preventive analgesia is the most likely explanation.³⁵

Treatment Modalities

The postoperative management of acute post-craniotomy pain involves multimodal analgesia with an armamentarium of drugs comprising opioids and nonopioids such as paracetamol, NSAIDs, dexmedetomidine, and gabapentinoids. Transdermal patches have also been used at a few centers as adjuvants.

Opioids

Opioids are highly potent analgesic agents used for the management of moderate to severe pain in all types of surgical procedures. Codeine, morphine, tramadol, fentanyl, and remifentanyl are used for pain management in neurosurgery patients via different routes of administration such as oral, subcutaneous (SC), intramuscular (IM), and intravenous (IV) route. These agents are described briefly in the following paragraphs.

Codeine

Codeine phosphate has been used as a first-line agent for the management of post-craniotomy pain and has been found to be used in 71% of the neurosurgical centers in the UK in one survey. It is preferred over other opioids due to various advantages including ceiling effect to respiratory depression, lack of sedation, and no effect on the postoperative neurological assessment and pupillary assessment.^{36,37} The disadvantages are less-potent analgesics as compared to morphine, ceiling effect to analgesic action, variable metabolism, and nonavailability of intravenous formulation.^{38–40}

Tramadol

It is a synthetic analogue of codeine. It is a weak opioid with a limited μ -opioid receptor affinity. It acts on pain through other pathways such as modification of the reuptake of norepinephrine and 5-hydroxytryptamine.⁴¹ Its advantages in neurosurgical patients are its limited sedative and respiratory effects. However, it has a higher propensity to cause postoperative nausea and vomiting (PONV), which has been found to be deleterious in neurosurgical patients and hence is used as a third- or fourth-line drug.³⁶ A study has, however, found it to be beneficial as a supplemental analgesic in post-craniotomy patients.⁴²

Morphine

Morphine is a highly potent opioid analgesic; however, in the UK, only 30% of the neurosurgical centers use it as a first-line analgesic agent in neurosurgical patients due to its feared side effects such as sedation, respiratory depression, and nausea and vomiting.⁴³ Morphine 10 mg was administered via intramuscular injection in a study and was not found to be associated with sedation, respiratory depression, or pupillary constriction in any of the neurosurgical patients.⁴⁴

Another route via which morphine can be administered postoperatively in neurosurgical patients is by the use of PCA pumps. Patients with this technique can titrate their own opioid boluses depending on their pain intensity. Various studies conducted using morphine PCA pumps in post-craniotomy patients did not find any delay in neurologic assessment, respiratory complications, or PONV. Thus, morphine administration via the PCA route is a safe technique that provides good analgesia, allows patient's control over their own pain management, decreases their psychological stress, decreases overall opioid requirement, and is devoid of any side effects.^{45–47}

Fentanyl and Remifentanyl

Fentanyl is an intermediate-acting and potent opioid used extensively in anesthesia. Remifentanyl is a potent and rapidly acting opioid with a short context-sensitive half-life with benefits of rapid emergence and hence early postoperative neurological assessment. In contrast, it is known to be associated with hyperalgesia and increased pain in the postoperative period.^{48–51} These agents have been compared in various studies. The time to first request for analgesia (median) was significantly shorter in the remifentanyl group when compared with the fentanyl group in one study

($p < 0.001$).⁵² Another study comparing the use of remifentanyl and piritramide with fentanyl also found a higher number of patients demanding rescue analgesia in the remifentanyl group.⁴⁸

Non-Opioid analgesics

Paracetamol

Paracetamol is a centrally acting cyclooxygenase inhibitor drug that has been found in a survey in the UK to be the second-line analgesic agent used in post-craniotomy patients.⁴³ It has a limited opioid-sparing effect with a meta-analysis concluding a reduction in the postoperative requirement of morphine by 20% with the use of paracetamol during the first 24 hours.⁵³ In a recent RCT, the use of IV acetaminophen 1000 mg, as adjunctive therapy for pain management in craniotomy patients, did not have any opioid-sparing effect during the 24 hours postoperative period but was associated with significantly higher patient satisfaction scores regarding the overall pain management.⁵⁴ Hence, it should be administered along with more potent analgesics.⁵⁵ Its advantages are that it does not cause sedation or respiratory depression and has a lower incidence of PONV, which are all hazardous in neurosurgical patients.⁵⁶

NSAIDs

A survey on post-craniotomy analgesia practices in the UK found NSAIDs to be used in 52% of the neurosurgical centers. These were prescribed regularly in 19% of the centers with the first dose administered on an average of 24 hours postoperatively.⁴³ Very few studies have been conducted on the use of these agents in neurosurgery patients.^{35,57} In one study, they found a statistically significant reduction in pain scores as well as the requirement of rescue analgesia in the flupirtine and diclofenac groups when compared with placebo with no significant difference in adverse effects such as nausea, vomiting, bleeding or constipation.⁵⁷

A major concern regarding the use of NSAIDs is their increased propensity to cause bleeding due to their anti-platelet function, which might lead to the development of a postoperative hematoma. A total of 2.2% of the neurosurgical patients were found to develop intracranial hematoma, of which 90% of patients developed hematoma within the first 6 hours after surgery, while 10% of patients developed it 24 hours after the surgery.⁵⁸ However, in a recent study, by Rajkiran et al., diclofenac sodium in a dose of 1.5 mg/kg given 30 minutes before the end of surgery and at 12-hour intervals postoperatively up to 48 hours was found to provide more effective analgesia at 24 hours postoperatively with significantly lower NRS scores as compared with paracetamol. They also found no differences in ACT, clot rate, and platelet function when analyzed using a Sonoclot analyzer, 24 hours after surgery in patients receiving diclofenac, and no patient had evidence of significant tumor bed hematoma on CT scan at 24 and 48 hours postoperatively.⁵⁹

NSAIDs have also been implicated as a common cause of renal failure in the postoperative period. This may be due to

renal blood flow becoming 'prostaglandin-dependent' in the state of hypovolemia as well as in the presence of high concentrations of circulating vasoconstrictors.⁶⁰ Thus, these agents must be used judiciously in certain high-risk patients for renal failure.

Cyclooxygenase 2 (COX-2) inhibitors are found to possess limited analgesic and opioid-sparing effects in various studies. Parecoxib has no antiplatelet effect and hence it does not increase the risk of bleeding, which is advantageous over other NSAIDs (41). Inj. parecoxib 40 mg was found to significantly decrease the VAS score at 6 hours after surgery and decreased morphine requirement for 6 to 12 hours after surgery.⁶¹ However, another RCT using parecoxib found no significant difference in pain intensity ($p=0.72$) and morphine consumption ($p=0.38$) in the first 24 hours after surgery.⁶² Increased risk of cardiovascular events has been described with long-term use; however, no such risk with acute administration has been documented.⁶³

Dexmedetomidine

It is a highly selective α -2 agonist with anti-nociceptive actions via both central and peripheral α -2 receptor binding. It has been used in post-craniotomy pain management as an adjuvant drug in scalp infiltration and scalp block.²⁹ Dexmedetomidine (0.2 to 0.7 μ g/kg/h) administered intravenously was found to significantly decrease the VAS score and opioid consumption in a study.⁶⁴

Gabapentinoids

Pregabalin is a structural analog of gamma-aminobutyric acid with anxiolytic, analgesic, and anticonvulsant effects.⁶⁵ A recent study found that 150 mg of pregabalin is effective as a pre-emptive analgesic agent for supratentorial tumor surgeries to decrease the postoperative opioid requirements.⁶⁶ Another study by Shimony et al in patients undergoing elective neurosurgical procedures also concluded that perioperative use of 150 mg pregabalin given twice daily attenuated preoperative anxiety, improved quality of sleep, and significantly reduced postoperative pain scores and requirement of analgesics without increasing the adverse effects.⁶⁷

Dexamethasone

Dexamethasone is an inexpensive long-acting glucocorticoid (half-life = 36–72 hours) and has potent anti-inflammatory properties with both local and systematic actions due to the alteration of inflammatory mediators and afferent nociceptive signaling mechanisms.⁶⁸ Perineural dexamethasone prolongs the duration of analgesia of peripheral nerve blocks by reducing the absorption of local anesthetics by causing vasoconstriction as well as by decreasing the activity of C fibers by inhibiting potassium channels.⁶⁹ It also reduces the peritumoral vasogenic edema and resultant increased intracranial pressure in patients with brain tumors.⁷⁰

A recent study has used dexamethasone as an additive in pre-emptive incision-site infiltration along with 0.5% ropi-

vacaine in patients undergoing supratentorial craniotomies.⁷¹ They found that the addition of dexamethasone to ropivacaine reduced the consumption of opioids by 27% and the postoperative pain scores 72 hours after craniotomy.

Gaudray et al in a study found that pre-emptive bilateral scalp nerve block with ropivacaine 0.75% administered along with 8 mg of IV dexamethasone provided good postoperative analgesia and significantly reduced the need for rescue analgesics in the first 48 hours ($p=0.006$).⁷² The REDUCE trial to study the effects of dexamethasone as an additive to bupivacaine in scalp nerve block in patients without the background of perioperative glucocorticoid administration is underway.⁷³

Transdermal Patch

A case report has described the role of a transdermal fentanyl patch along with continuous paravertebral anesthetic infusion using an On-Q Pain-Buster catheter system in a patient undergoing posterior occipitocervical junction surgery with good postoperative pain relief.⁷⁴ In the future, more studies are to be planned using this mode of drug delivery to assess its efficacy in neurosurgical patients.

Chronic Post-craniotomy Pain

Chronic post-craniotomy pain, also known as persistent headache attributed to craniotomy of more than 3 months duration. Diagnostic criteria of chronic pain include any headache that develops within 7 days after one of the following: craniotomy, regaining of consciousness after the craniotomy, or discontinuation of medications that impair the ability to sense as well as report headache after craniotomy and persists for more than 3 months following the craniotomy.¹ It should not be better accounted for by another ICHD-3 diagnosis.

The incidence of chronic post-craniotomy pain is higher after infratentorial surgeries as compared with supratentorial surgeries. Harner et al studied acoustic neuroma patients and reported a 23% incidence of headache at 3 months that dropped to 16% at 1 year and 9% at 2 years.¹⁵ Jackler et al have reported the persistence of headaches for more than 6 months in 29% of patients who underwent acoustic neuroma surgery.⁷⁵ In patients undergoing supratentorial craniotomy, 17.5% of patients experienced headaches beyond 2 months, 5.6% of patients between 2 months and 1 year, and 11.9% of patients suffered from headaches even 1 year after surgery.

Pathophysiology

The mechanisms behind chronic pain are complex and still remain unclear on the molecular level. These include sensitization of central neurologic pain perception, structural changes in neurons in the central nervous system, hyperstimulation of γ -Aminobutyric acid (GABA) receptors in the raphe nuclei, and changes in the serotonergic and hemodynamic systems. There is also a potential role of catecholaminergic nerves in patients suffering from chronic pain.⁷⁶

Presentation and Causes of Chronic Post-craniotomy Pain

Post-craniotomy pain has been classified into the following types based on their resemblance to naturally occurring headaches.⁷⁷

Syndrome of post-traumatic Headache

When craniotomy is performed for the treatment of intracranial pathology occurring secondary to trauma, it may lead to chronic pain along with cognitive, somatic, and behavioral manifestations. Such headaches if persisting for more than 2 months are called chronic post-traumatic headaches. They manifest as chronic tension-type headaches or as migraine-like attacks and over time may follow a daily occurrence pattern.^{78,79}

Chronic Tension-type Headache associated with Analgesic Abuse

This occurs as rebound headaches in patients with overuse of analgesic medications. These patients have psychiatric comorbidities such as stress disorder, depression, insomnia, and alcohol and drug abuse, which may complicate management.⁶⁰

Cervicogenic Headache

This occurs in patients with degenerative disease of the upper cervical spine. These patients develop tension-type pain due to their position during surgery, e.g., posterior fossa surgery.⁸⁰ Increased tension in pericranial muscles may also aid in the development of these headaches.⁸¹

Chronic Headache due to Scar Tissue Formation

This occurs secondary to scar tissue formation surrounding the occipital nerves or due to fibrous adhesions that bind the neck muscles directly to the dura. These neck muscles may pull the dura during neck movements resulting in pain.⁸²

Headache due to Occipital Nerve Entrapment or Neuralgia

Direct sectioning of occipital nerves or stretch injury secondary to retraction with neuroma formation may result in these headaches.⁸³

Seizure-associated Headaches

These are tension or migraine-like headaches occurring frequently in patients with partial and generalized seizures.⁸⁴ Their treatment must target the headache syndrome along with the basic principles for treating primary headaches.⁸⁵

Orthostatic Headaches

These occur secondary to CSF leaks or shunt-over drainage. Patients may present with nausea, vomiting, pain or tightness around the neck, dizziness, diplopia, photophobia, binasal visual field defects, and hearing disorders. Patients may have immeasurable, very low, or normal CSF opening pressures. They respond well to surgical management with complete symptom resolution.⁸⁶

Neuropathic Headaches

These patients exhibit symptoms of neuropathic pain such as hyperalgesia and allodynia over the scar and require early and aggressive treatment.⁸⁷

Management of Chronic Post-craniotomy Pain

Assessment

Chronic post-craniotomy pain has been divided into four grades based on severity.⁸⁸ Grade-1 patients have minor annoyance, grade-2 headaches are present nearly every day, grade-3 patients require medicines every day, and patients with grade-4 headaches feel incapacitated. Assessment of chronic headache can be done using the McGill Pain Questionnaire and the Brief Pain Inventory scoring system.²⁵

Management

Patients with chronic pain can be managed with various combinations of non-pharmacological and pharmacological therapies which are described in ►Tables 2 and 3.

Conclusion

Post-craniotomy pain is usually undertreated in neurosurgical patients. With the availability of the aforementioned modalities in the diagnosis and perioperative management, the neuroanesthesiologists must act hard utilizing the available diagnostic and multiple treatment modalities available

Table 2 Management of chronic post-craniotomy headache

Nonpharmacological ⁶¹	Pharmacological
TENS Physiotherapy Acupuncture ⁸³ Cognitive behavior therapy Stress management techniques (relaxation) Neck collars Manual neck traction Radio frequency nerve ablation Cryoablation	Analgesics ⁶¹ Paracetamol Codeine NSAIDS
	Tricyclic antidepressants Amitriptyline ⁸⁹
	Anticonvulsants Carbamazepine ⁹⁰ Sodium valproate ^{91,92} Gabapentin ⁹³⁻⁹⁵ Lamotrigine ⁹⁶
	Sodium channel Blockers Lignocaine ⁹⁷
	Sumatriptan ⁸³
	Trigger-point injections ⁶¹
	Topical Capsaicin ⁶¹
	Botulinum toxin type A ⁶¹
	Surgical techniques ⁹⁸⁻¹⁰⁰ C2 gangliotomy C2 ganglionectomy C2 to C3 rhizotomy C2 to C3 root decompression Distal neurectomy
	Neurolysis ^{101,102}
	Occipital nerve stimulation ¹⁰³

Table 3 Pharmacological and surgical management of chronic post-craniotomy headache

Drugs	Mechanism of action	Uses	Side effects
Tricyclic antidepressants			
Amitriptyline ⁸⁹	Presynaptically inhibit reuptake of norepinephrine and serotonin. NMDA receptor antagonists Weak mu opioid receptor agonists Na ⁺ and Ca ²⁺ channel blockers. Act postsynaptically on cholinergic, α -adrenergic, and histamine receptors	Co-analgesics in treatment of chronic headache	Sedation Anticholinergic symptoms
Anticonvulsants			
Carbamezepine ⁹⁰	Slows rate of recovery of voltage-gated Na ⁺ channels Minor Ca ²⁺ channel antagonist effect	Trigeminal neuralgia Neuropathic headaches	Dizziness Hematological disorders
Sodium valproate ^{91,92}	↑ GABAergic transmission ↓ Release and/or effects of EAA Na ⁺ channel blocker Dopaminergic and serotonergic transmission modulation.	Migraine-like headaches related to craniotomy Post-traumatic injury headaches	Gastrointestinal disturbances Tremors Weight gain Platelet disorders Liver toxicity Pancreatitis Encephalopathy
Gabapentin ⁹³⁻⁹⁵	Acts on GABA(B) receptors Binds to $\alpha_2 \delta$ subunit of voltage gated Ca ² channel resulting in decreased Ca ² influx into nerve terminal Regulates synaptic and extrasynaptic NMDA receptors.	Neuropathic pain Allodynia or hyperalgesia over the scar region	Transient side effects Mild to moderate dizziness Somnolence
Lamotrigine ⁹⁶	Blocks voltage-dependent Na ⁺ channels Inhibits glutamate release	Trigeminal neuralgia Chronic pain subsequent acoustic neuroma surgery Used in refractory cases	Dizziness, constipation, nausea and drowsiness. Skin rash and allergic reactions
Sodium channel blockers			
Lignocaine ⁹⁷	Suppresses discharge of ectopic impulses generated at sites of experimental nerve injury as well as in axotomized dorsal root ganglion (DRG) cells	Topically-gel and patches Trigger point injections in cervicogenic headache	
NSAIDs and paracetamol ⁶¹	Inhibition of prostaglandins - decreases pain and inflammation	Chronic post traumatic headache	Bleeding disorders Renal defects
Sumatriptan ⁸³	5-HT ₁ agonist, selectively targeting 1 _B and 1 _D receptors. Reduces pain signal transmission in the trigeminal dorsal horn.	Persistent headache following excision of acoustic neuroma migraine type of headache	Dizziness and sedation Triptan sensations-burning or tingling in the chest or limbs Serotonin syndrome if taken with SSRIs and SNRIs
Capsaicin ⁶¹	Depletion of substance P from the primary afferent neurons	Allodynia Hyperalgesia over scar	Burning sensation
Botulinum toxin type A (Botox A) ⁶¹	Direct skeletal muscle-spasmodolysis	Chronic pain due to increased muscle tone	
Surgical management			
Destructive surgeries ⁹⁸⁻¹⁰⁰ C2 gangliotomy C2 ganglionectomy		Occipital neuralgia.	Painful neuroma Intractable neuropathic pain Causalgia

(Continued)

Table 3 (Continued)

Drugs	Mechanism of action	Uses	Side effects
C2 to C3 root decompression C2 to C3 rhizotomy Distal neurectomy			
Neurolysis of the greater occipital nerve ^{101,102}		Chronic headaches caused by occipital neuralgias	
Occipital nerve stimulation ^{103,104}	Similar to that of gate control theory	Cervicogenic headache, Occipital neuralgia and other chronic types of headaches	

in our armamentarium and act fast (at the earliest possible) in such patients for the management of post-craniotomy pain. As true with the management of post-surgical pain in other surgeries, the patients respond best to multimodal treatment options, especially a combination of pharmacological agents and local anesthetics. A combination of pharmacological agents (NSAIDs, judicious opioids, and other adjuvant drugs) and scalp blocks or wound infiltration are viable options to manage post-craniotomy pain. Aggressive management of post-craniotomy pain may help in reducing the incidence of chronic post-craniotomy headaches.

Conflict of Interest

None declared.

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