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## Review in The Management of Post-Craniotomy Pain

Pain can lead to increase in the sympathetic stimulation and thereby cause hypertension and rebleed in the operative site. The ideal management of pain in these circumstances is a topic of debate worldwide. The standard algorithm for pain management is usually with nonsteroidal anti-inflammatory drugs (NSAIDs) with or without opioids. Good pain management helps to reduce not only the pain but also shortens hospital stay and cost and leads to early recovery but overenthusiastic use of drugs can lead to sedation, mydriasis, respiratory depression which could increase the intracranial pressure or obtundation of deteriorating neurological signs. There is thus no Gold Standard drugs or algorithm to manage post craniotomy pain and this review aims to discuss the common availability of medicine and review the various options available for successful management of post craniotomy pain (PCP). Each neurosurgical centre must have a protocol and guidelines regarding PCP management which will be easier for the juniors and nurses to follow. Multimodality treatment can achieve best results and further controlled trials with the different medications alone or in combination, studies in cannabinoid derivatives in future can help to formulate and ideal PCP management algorithm.

**Key words:** Craniotomy, Opioid, NSAIDs, Nerve block, Morphine, Gabapentin, Post-Craniotomy headache

**A**ny surgical intervention leads to pain and thus the latter management is also a key factor in improving the overall outcome in neurosurgery. Craniotomy is the most common neurosurgical procedure worldwide for almost all types of neurosurgical diseases and thus is the commonest cause of headache and pain in these cases. Postoperative pain causes a great deal of alarm, concern, anxiety, doubt in treatment, feeling of failure and even depression in patients. This type of pain is found to be commoner in females and younger

patients.<sup>23</sup>The International Headache Society has defined post-craniotomy headache as that developing within a week after surgery and lasting till 3 months in Acute and beyond 3 months in chronic type.

Pain can lead to increase in the sympathetic stimulation and thereby cause hypertension and rebleed in the operative site. The ideal management of pain in these circumstances is a topic of debate worldwide. The exact incidence of pain postoperatively varies because it also depends on the type of surgery, the counselling,

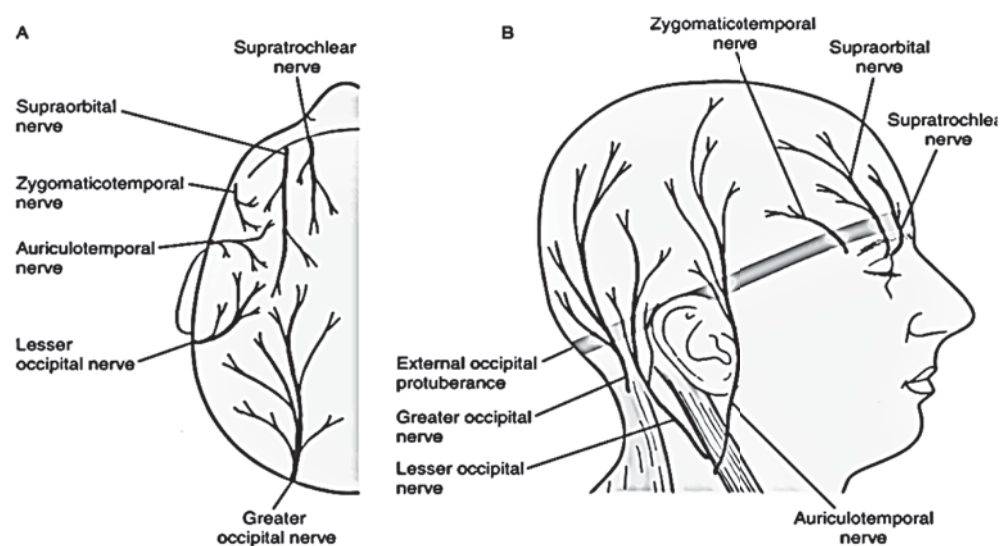


Figure 1. The sensory supply of the scalp and the potential sites for nerve block.<sup>15</sup>

the psychology of the patient and the perioperative analgesia used. In one of the earliest studies pain was found to be moderate to severe in around 60%.<sup>6,8,28</sup> The standard algorithm for pain management is usually with nonsteroidal anti-inflammatory drugs (NSAIDs) with or without opioids.<sup>36</sup> Good pain management helps to reduce not only the pain but also shortens hospital stay and cost and leads to early recovery but overenthusiastic use of drugs can lead to sedation, mydriasis, respiratory depression which could increase the intracranial pressure or obtundation of deteriorating neurological signs. There is thus no Gold Standard drugs or algorithm to manage post craniotomy pain and this review aims to discuss the common availability of medicine and review the various options available for successful management of post craniotomy pain (PCP).

#### The post-craniotomy pain pathogenesis:<sup>7,28</sup>

PCP is typically a dull aching pain, mingling with headache, either localized to the incision site or a headache which is pulsating, tightening, band like which is aggravated by coughing, sneezing, exercise or head or neck movement. It may be associated with nausea, vertigo, tinnitus and photophobia. The pain is somatic and due to the dissection of the muscles and tissues and is more severe in surgery of the posterior fossa and subtemporal region where more extensive dissection of the thick muscles is needed. Excessive traction, cautery, dural tension, aseptic meningitis, bone dust, muscle or vascular manipulation in the scalp can increase the pain. Localized cerebrospinal fluid (CSF) collection also leads to features of meningism and headache. Females and the younger population are more prone for PCP while males and elderly are comparatively better tolerant to pain.<sup>2</sup> Females

had 40% more incidence of headaches and majority of them rated that as severe.<sup>11</sup> PCP is maximum 48 hours after surgery and one third may still have pain beyond this time. The International Headache Society has defined postcraniotomy headache as that developing within a week after surgery, regaining of consciousness after surgery and discontinuation of medication(s) impairing ability to sense or report headache following the craniotomy, and lasting till 3 months in Acute and beyond 3 months in Chronic type provided other causes of headache are excluded.<sup>37</sup> Chronic PCP is usually associated with surgery of acoustic neuroma and last till a year.<sup>29</sup>

#### Options in the Prevention of PCP

Local scalp infiltration, non-pharmacological treatment, pharmacological treatment and surgical methods are the options available for PCP control.

#### Scalp infiltration:

The scalp has an extensive network of sensory nerves and their manipulation during surgery can lead to further central sensitization leading to enhanced pain perception in future. Infiltration of some drugs like Bupivacaine 0.5% or Ropivacaine with or without Lidocaine has been found to significantly reduce PCP without any side effects and last till 48 hours.<sup>11,13,14,26,36</sup> This can be supplemented with nerve blocks like maxillary nerve block, for further pain control. Figure 1 shows the nerves supplying the scalp where blocks can be made.

#### Surgical Techniques to reduce PCP<sup>18,27,35,33</sup>

Numerous steps taken during surgery can lead to significant reduction of PCP. Clean and neat dissection, without excessive use of cautery, retraction, muscle manipulation and removal of bone dust can also reduce

Drug	Starting doses and intervals	
	<50 kg (mg·kg <sup>-1</sup> )	>50 kg and adult (mg flat dose)
Ketorolac	0.5 mg·kg <sup>-1</sup> IM/IV Q 6 H, up to maximum of 72 h <sup>a</sup>	15–30 mg Q 6 H, not to exceed 120 mg·day <sup>-1</sup> , up to a maximum of 72 h
Ibuprofen	5–10 mg·kg <sup>-1</sup> PO; not to exceed 40 mg·kg <sup>-1</sup> ·day <sup>-1a</sup>	200–800 mg PO Q 6 H
Acetaminophen	<p>Oral</p> <p>Neonates</p> <p>Dose: 10–15 mg·kg<sup>-1</sup> PO q6–8h</p> <p>Max: 60 mg·kg<sup>-1</sup>·day<sup>-1</sup></p> <p>Infants/children</p> <p>Dose: 10–15 mg·kg<sup>-1</sup> PO q4–6h</p> <p>Max: 75 mg·kg<sup>-1</sup>·day<sup>-1</sup> up to 1 g per 4 h and 4 g·day<sup>-1</sup></p> <p>&gt;12 years</p> <p>Dose: 325–650 mg PO q4–6h</p> <p>Max: 1 g per 4 h and 4 g·day<sup>-1</sup></p> <p>IV</p> <p>12.5 mg·kg<sup>-1</sup> IV Q 4 H</p> <p>OR</p> <p>15 mg·kg<sup>-1</sup> IV Q 6 H</p> <p>Not to exceed 750 mg per dose and 80 mg·kg<sup>-1</sup>·day<sup>-1</sup></p>	<p>Oral</p> <p>325 mg PO Q 4 H-Q6H</p> <p>OR</p> <p>500 mg PO Q 6–8 H</p> <p>OR</p> <p>625 mg PO Q 8 H</p> <p>Not to exceed 4 g·day<sup>-1</sup></p> <p>IV</p> <p>650 mg IV Q 4 H</p> <p>OR</p> <p>1000 mg IV Q 6 H</p> <p>Not to exceed 4 g·day<sup>-1</sup></p>
Clonidine	<p>Oral and transdermal</p> <p>1 µg·kg<sup>-1</sup>·dose<sup>-1</sup> Q 4 H PO</p>	<p>Oral and transdermal</p> <p>1 µg·kg<sup>-1</sup>·dose<sup>-1</sup> Q 4 H PO</p>
Diazepam	<p>Oral</p> <p>0.25–0.3 mg·kg<sup>-1</sup> Q 6–8 h</p> <p>IV</p> <p>0.05–0.1 mg·kg<sup>-1</sup> Q 4–6 H</p>	<p>Oral</p> <p>2–10 mg·kg<sup>-1</sup>·day<sup>-1</sup> Q 6–8 h</p> <p>IV</p> <p>2–10 mg IV/IM Q 3–4 H</p> <p>No more than 30 mg per 8 h</p>
Gabapentin	<p>3–12 years</p> <p>10–15 mg·kg<sup>-1</sup>·day<sup>-1</sup> divided Q 8 H</p> <p>&gt;12 years</p> <p>300 mg PO Q 8 H, may increase up to 600 mg PO Q 8 H</p>	<p>300 mg PO QHS, then gradually increase as tolerated to 300 mg Q 8 H</p>
Amitriptyline	<p>Load</p> <p>0.1 mg·kg<sup>-1</sup> PO QHS; increase as tolerated over 2–3 weeks</p> <p>Maintenance</p> <p>0.5–2 mg·kg<sup>-1</sup> PO QHS</p>	<p>Load</p> <p>75 mg·day<sup>-1</sup> PO</p> <p>Maintenance</p> <p>150–300 mg·day<sup>-1</sup> orally in single or divided doses</p>

<sup>a</sup>Safety of nonsteroidal antiinflammatory drugs (NSAIDs) such as ketorolac or ibuprofen in children less than 3–6 months of age is not well established.

Figure 2. Showing the dosage of non opioidal analgesics that are commonly used for PCP relief.<sup>34</sup>

PCP. Bone flap replacement cause significantly less PCP than craniectomy at discharge and one-year follow-up. Watertightdural closure with reduced CSF leak is a possible cause for the reduced PCP. Studies have found insertion of bone cement, adipose tissue graft and use of augmentation duraplasty showed reduction of PCP.

**Pharmacological treatment of PCP**

An ideal neurosurgical analgesic medication should be able to give good relief of pain, have anti-inflammatory properties, should not affect the central nervous system functions, hinder consciousness or neurological assessment, shouldn't cause cardio-respiratory depression, is not addictive and with no side effects like vomiting, nausea, epilepsy or local bleeding. Sadly, there is no drug that fits this category and hence neurosurgeons worldwide have to rely on different medications in isolation of in combination for PCP management. In a study from UK it was found that only 65% of neurosurgical centres had analgesic protocols and over the decades Morphine was the first line analgesic used followed by paracetamol

(84%) and NSAIDs (52%). Codeine use reduced from 90% to 70% over the same time period.<sup>19,30</sup>

**Non-Opiod Analgesics/ NSAIDs (Figure 2)**

**Paracetamol/ Acetaminophen:** this has been used alone or in a combination to reduce PCP. The exact mechanism of action is unclear although it may act by Beta-Endorphin receptor modulation, prostaglandin H2 receptor synthetase or a central nervous painkiller action. Patient with liver disease are cautioned. Acetaminophen also acts by inhibiting COX-3 inhibition and descending serotonergic pathways. It has minimal anti-inflammatory and antiplatelet effect and at doses of 10-15 mg per Kg has few serious side effects. It can be given intravenous, orally or in pediatric patients per rectally(at a higher dosage of 25-40 mg per Kg).<sup>1,4</sup> It has been used with Sufentanil combination with better PCP control.

**NSAIDs:** these are another group of very commonly used analgesics (ibuprofen, diclofenac, Naprosyn, ketorolac) which reduce PCP, reduce inflammation and has no opioid like side effects. These act as cyclooxygenase

Drug	Parenteral/oral ratio	Starting doses and intervals	
		<50 kg (mg·kg <sup>-1</sup> )	>50 kg and adult (mg flat dose)
<b>(a) Oral agents</b>			
Oxycodone	N/A	0.1 mg·kg <sup>-1</sup> Q 3–4 h	5–10 mg Q 3–4 h
Morphine			
Immediate release	1 : 3	0.3 mg·kg <sup>-1</sup> Q 3–4 h	15–20 mg Q 3–4 h
Sustained release	1 : 5	Flat dose only!! 20–35 kg: 10–15 mg Q 8–12 h 35–50 kg: 15–30 mg Q 8–12 h	30–45 mg Q 8–12 h
Hydromorphone	1 : 2–1 : 4	0.03–0.08 mg·kg <sup>-1</sup> Q 3–4 h	1–2 mg Q 3–4 h
Methadone	1 : 1–1 : 2	0.2 mg·kg <sup>-1</sup> Q 4–8 h	10 mg Q 4–8 h
Codeine		NR <sup>a</sup>	30–60 mg Q 3–4 h
<b>(b) Parenteral agents</b>			
Drug	Equianalgesic IV dose (mg)	<50 kg (mg·kg <sup>-1</sup> )	>50 kg and adult (mg flat dose)
Fentanyl	0.1	0.5–1.0 µg·kg <sup>-1</sup> Q 1–2 h	25–50 µg·kg <sup>-1</sup> q1–2 h
Morphine	10	Bolus 0.05–0.1 mg·kg <sup>-1</sup> Q 1–2 h Infusion 0.025 mg·kg <sup>-1</sup> ·h <sup>-1</sup>	Bolus 2.5–5 mg Q 0.5–2 h Infusion 1–2 mg·h <sup>-1</sup>
Hydromorphone	1.5–2	Bolus 0.015 mg·kg <sup>-1</sup> Q 1–2 h Infusion 2–4 µg·kg <sup>-1</sup> ·h <sup>-1</sup>	Bolus 1 mg Q 1–2 h Infusion 0.2–0.3 mg·h <sup>-1</sup>
Methadone	10	0.1 mg·kg <sup>-1</sup> Q 4–8 h	5–10 mg Q 4–8 h
Meperidine	75–100	NR <sup>b</sup>	NR

<sup>a</sup>Due to the FDA black box warning against use of this drug in postop pediatric T&A patients, and evidence of pharmacogenetic metabolic variation, the use of this drug is not recommended for pediatric neurosurgical patients (49–51).

<sup>b</sup>Meperidine is metabolized to normeperidine which can cause seizures.

Figure 3. Showing the common opioidal drugs and their dosage. <sup>34</sup>

2 inhibitor (COX) and can cause platelet dysfunction and increase bleeding (COX-1 isomer) and analgesia by (COX-2 isomer). Selective COX-2 inhibitor does not have anti-platelet effects and therefore do not cause bleeding. The effectiveness of COX-2 inhibitors (parecoxib, rofecoxib) in relieving pain has been well proven in other surgical specialities.<sup>3,16</sup> In a study of the use of parecoxib 40 mg in craniotomy patients it was found to decrease pain score and morphine use but with no significant analgesia effect.<sup>17</sup> The limitations of the COX-2 inhibitors are the potential to cause myocardial infarction which was shown in the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial leading to withdrawal of rofecoxib. COX-2 inhibitors also inhibit important renal prostanoids leading to hyperkalemia, salt retention, hypertension with potential increase of heart failure.<sup>32</sup>

**Dexmedetomidine:** is a selective alpha2-adrenergic agonist acting at central and peripheral level as a non-opioid analgesic. There are several studies that has shown the beneficial effect of this drug in PCP with good pain control, reduced use of postoperative morphine although time to extubation was not different. Bradycardia can be a significant side effect of using this drug and lead to a cause of alarm in postoperative period.<sup>25</sup>

**Gabapentinoids:** these are analgesics that act via the Alpha2-delta subunit of N-type voltage gated Calcium

channels by reduction in excitatory neurotransmission. They also have opioid sparing effects and few studies have shown the beneficial effects of single dose of preoperative gabapentin. Gabapentin was first used as an anti-epileptic for partial seizures. Pregabalin which is a gabapentin derivative has also analgesic and anti-epileptic properties. Further trials are needed using this drug and its results in PCP management. The most common side effects of this drug are peripheral edema, giddiness, drowsiness and ataxia.<sup>5,22</sup>

**Dexamethasone:** can reduce inflammation and thus help in reducing pain. This has been used to reduce ICP and along with Gabapentinoids or Phenytoin to manage PCP.<sup>22</sup>

**NMDA receptor antagonist:** Methadone and Ketamine can cause analgesia as an NMDA receptor antagonist and can be used in single or with NSAIDs or opioids perioperatively. It has opioid sparing property and has been used in spine and other non-neurosurgical procedures. Ketamine has the potential for raising ICP and thus studies are limited regarding its use in PCP management.<sup>20</sup>

**Other Miscellaneous:** Amitriptyline, diazepam, sodium valproate, carbamazepine and clonidine are some other drugs used for pain management.

Opioid Analgesic [Greek “opion-poppy plant juice”]



**Tramadol:** the classical side effects of opioids like sedation, dizziness, vomiting, dry mouth, nausea, vomiting, miosis can hide the true signs of neurological deterioration and hence the use of opioids was not common in neurosurgery. Tramadol is a weak analgesic acting as the Mu-receptor agonist or serotonin/ norepinephrine reuptake inhibition. It does not affect coagulation or platelet function and hence is theoretically safe in neurosurgery. Tramadol use has shown not only to reduce the hospital stay by 24 hours but also the overall cost of analgesics used by 32 US \$.<sup>38</sup> Long term use can lead to physical dependence and even withdrawal syndrome like hallucination, anxiety, panic attack, paresthesia and numbness usually within a day of stopping medication. Its use has been likened to that of heroin in high doses. Its use along with opioid analgesic and acetaminophen can further enhance PCP management.

**Narcotic drugs:** [Greek “narco- to deaden”] these include, morphine, hydrocodone, remifentanyl, codeine, fentanyl, oxycodone and propoxyphene. They act by stimulating, mu (morphine), kappa and sigma subtype opioid receptors in the peripheral and central nervous system. The mu receptor depending on the site and function are further divided into mu1-supraspinal analgesia, mu2- gastrointestinal motility inhibition and respiratory depression and mu3-that act on leukocytes and have anti-inflammatory actions.<sup>24</sup> The important side effects like respiratory depression is a major deterrents of the use of opioids in neurosurgery and thus used only for short duration based on the individual hospital protocol. They can be used as bolus, intravenous infusions, patient-controlled devices or as needed basis *pro re nata* with equal efficacy. It can be converted to oral dosage once patient stabilizes. Intramuscular route is also used but has the disadvantage of slower absorption and delayed action. Fentanyl when compared with morphine is fast acting, lipophilic and has a shorter duration of action and can also be used as a transdermal patch or transmucosal/transnasal route. The transmucosal/nasal route by passes the first-pass hepatic metabolism and thus is more efficient in PCP management. The skin condition, ethnicity, age, location and temperature can affect the transdermal route absorption and the drug can still be absorbed 24 hours even after the patch is removed. Remifentanyl is another potent rapid action drug and is associated with better hemodynamic control during induction and improved level of consciousness and has been studied for awake craniotomy.<sup>10</sup>

Use of capnography and inductance plethysmography helps in the early diagnosis and management of respiratory depression in those using continuous pump infusions. Oxycodone is preferred over codeine as it does not need the

cytochrome P450 2D6 isoenzyme to metabolize and hence is safer in those with the latter deficiency. Constipation needs special care as many of the neurosurgical patients are bedridden for a long time. Nausea and itching can also be severe in some cases. The dosage guidelines of the common opioids are given in Figure 3.<sup>34</sup>

**Management of chronic PCP:** these are a subtype of patients that complain of persistent headache or pain after craniotomy. Other causes like cervical spondylosis, psychiatric illness, fibromyalgia, migraines and tension headaches must be ruled out. NSAIDs are the first line drugs and if they are not helpful then amitriptyline, gabapentinoids, carbamazepine or sodium valproate can be used. Antiepileptics can help to control both postoperative seizures and treat headaches too. Local analgesia, steroid injections, Botox injections, removal of stitch scars are other interventions to relieve pain. If permissible Cannabis derived products have potential to treat chronic PCP.<sup>21</sup>

## Conclusion

PCP is a common problem in as many as 80% of cases have moderate to severe pain which may not be adequately treated as the brain is assumed to be insensitive to pain. Inadequate PCP management can lead to a multiple of problems like anxiety, hypertension, headache and post-operative bleeding. The proper management would thus involve perioperative nerve block with local incision site infiltration and good postoperative analgesia. The visual analog scale/ pain scale chart is useful tool to assess the PCP and decide on the type of analgesic to be used. The factors like age, sex, possible psychology, site of operation and metabolic diseases or clinical factors need to be considered. For mild pain, NSAIDs can be used as they are cheap, easily available, quick acting, minimal side effects of sedation or nausea/vomiting and do not alter the consciousness levels. They can be used alone or in combination. For severe pain opioids can be used in either continuous infusion, transdermal or transnasal or transmucosal routes. Patient controlled pain releasing devices are also useful where available. While trying to achieve a painless postoperative stay is important one must not forget the potential side effects of using analgesics which could be immediate or in future. Timely identification and management of complications of analgesics is as important as starting the medications. Topical analgesics, cold compression, transcutaneous electrical stimulation and psychological counselling can benefit in a subset of patients.

Each neurosurgical centre must have a protocol and guidelines regarding PCP management which will be easier for the juniors and nurses to follow. Multimodality

treatment can achieve best results and further controlled trials with the different medications alone or in combination, studies in cannabinoid derivatives in future can help to formulate an ideal PCP management algorithm.

The ideal plan of action would be Preoperative counselling with local nerve block of infiltration followed by Opioid analgesics on a continuous, bolus, or as per demand analgesia supplemented with paracetamol and followed up with gabapentinoids or amitriptyline for chronic pain can benefit patients with PCP.

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