

REVIEW ARTICLE

The postoperative management of pain from intracranial surgery in pediatric neurosurgical patients

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Summary

Pain following intracranial surgery has historically been undertreated because of the concern that opioids, the analgesics most commonly used to treat moderate-to-severe pain, will interfere with the neurologic examination and adversely affect postoperative outcome. Over the past decade, accumulating evidence, primarily in adult patients, has revealed that moderate-to-severe pain is common in neurosurgical patients following surgery. Using the neurophysiology of pain as a blueprint, we have highlighted some of the drugs and drug families used in multimodal pain management. This analgesic method minimizes opioid-induced adverse side effects by maximizing pain control with smaller doses of opioids supplemented with neural blockade and nonopioid analgesics, such as nonsteroidal antiinflammatory drugs, local anesthetics, corticosteroids, N-methyl-D-aspartate (NMDA) antagonists, α_2 -adrenergic agonists, and/or anticonvulsants (gabapentin and pregabalin).

Introduction

The treatment and alleviation of pain is a basic human right that exists regardless of age (1–3). The old ‘wisdom’ that young children neither respond to, nor remember, painful experiences to the same degree that adults do is simply untrue (4,5). Many, if not all, of the nerve pathways essential for the transmission and perception of pain are present and functioning by 24 weeks of gestation (6,7).

Nevertheless, the pain associated with neurosurgery has historically been undertreated because of the fear that the use of opioids may interfere with the neurologic examination or lead to its deterioration (8–10).¹ Much of

the information concerning the quality, duration, and treatment of pain following cranial surgery is anecdotal. Opioids, the analgesics most often prescribed for moderate-to-severe pain, may produce sedation and miosis and mask signs of intracranial catastrophe (11). Additionally, opioids, even when administered in therapeutic doses, may depress minute ventilation leading to hypercapnia, increased intracerebral blood volume, and potentially increased intracranial pressure and cerebral edema (12). Moreover, vomiting is a common side effect of opioids and an important symptom of increased intracranial pressure. Finally, why expose a patient to these risks when there is a presumed lack of need? Decades of training and anecdote have reinforced a widely held belief that patients do not experience intense pain following intracranial surgery, a belief supported by the fact that surgery on the brain parenchyma per se is not painful.

And yet, over the past 10 years, accumulating evidence has revealed that pain following craniotomy surgery is common and often very painful (8–10,13–15).¹ Neverthe-

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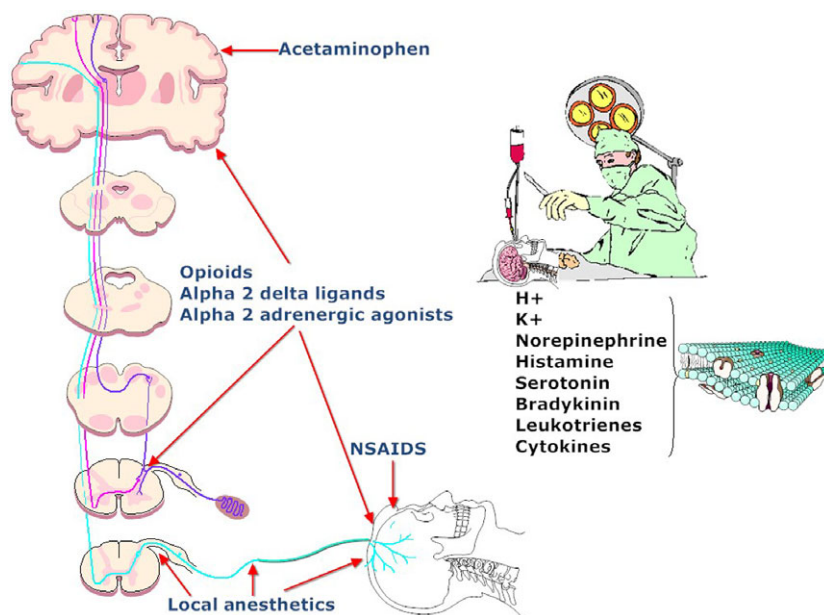


Figure 1 After an acute injury (neurosurgery), inflammatory mediators are released at the site of injury. These mediators lower the pain threshold at the site of injury (primary hyperalgesia) and in the surrounding tissues (secondary hyperalgesia). Nociceptive nerve

pathways are essential in the transmission, perception, and modulation of pain. Targets of multimodal drug modulation of pain along these pathways are depicted. This figure was drawn using SmartDraw software, 2014 Enterprise edition, San Diego, CA, USA).

less, how to treat this pain without affecting neurologic outcome remains a therapeutic conundrum (16). On the one hand, we want to alleviate pain and on the other is the need to do no harm. To treat pain without causing harm, we and others advocate the use of a multimodal approach (2,3,14,15). In this approach, smaller doses of opioid and nonopioid analgesics, such as nonsteroidal antiinflammatory drugs (NSAIDs), local anesthetics, N-methyl-D-aspartate (NMDA) antagonists, corticosteroids, anticonvulsants (gabapentin and pregabalin), α_2 -adrenergic agonists, are combined to maximize pain control and minimize drug-induced adverse side effects. In the following, we will update previously published reviews and will focus on the applicability of a multimodal approach in neurosurgical patients (2,3,17).

Pediatric pain assessment

It is beyond the scope of this review to adequately summarize how pain is assessed in infants, children, and adolescents. There are multiple reviews, monographs, textbooks, and online resources devoted to this topic (18–21). Nevertheless, the importance of pain assessment cannot be overstated: It is difficult to treat that which cannot be measured. Further, without measurement, it is difficult, if not impossible, to evaluate the efficacy and safety of therapies used in treatment.

Pain physiology

How pain is perceived is more than simply the transmission of noxious stimuli from a site of injury to the brain. Rather, the afferent and efferent pain neural pathways are integrated and given value within higher centers of the central nervous system (Figure 1). These pathways have been well described and are available in multiple review articles, text books, and online resources. Nevertheless, a thorough understanding how these pathways function and interact is crucial in formulating pain management strategies because they provide the targets of therapeutic interventions (Figure 1).

Essentially, following an acute injury such as surgical or accidental trauma, inflammatory mediators are released, which lower the pain threshold at the site of injury (primary hyperalgesia) and in the surrounding uninjured tissue (secondary hyperalgesia). These inflammatory mediators, which include hydrogen and potassium ions, histamine, leukotrienes, prostaglandins, cytokines, serotonin, bradykinins, and nerve growth factors, make a ‘sensitizing soup’ which together with repeated stimuli of the nociceptive fibers cause decreased excitatory thresholds and result in peripheral sensitization (Figure 1) (2,3,22).

As the primary afferent neurons enter the spinal cord, they segregate and occupy a lateral position in the dorsal horn. ‘Second-order’ neurons that receive

these chemical signals integrate the afferent input with facilitatory and inhibitory influences of interneurons and descending neuronal projections. It is this convergence within the dorsal horn that is responsible for much of the processing, amplification, and modulation of pain. Nociceptive activity in the spinal cord and the ascending spinothalamic, spinoreticular, and spinomesencephalic tracts carry messages to supraspinal centers (periaqueductal gray, locus coeruleus, hypothalamus, thalamus, and cerebral cortex) where they are modulated and integrated with autonomic, homeostatic, and arousal processes. This modulation, particularly by the endogenous opioids, gamma aminobutyric acid (GABA), and norepinephrine, can either facilitate pain transmission or inhibit it. Modulating pain at peripheral, spinal, and supraspinal sites helps achieve better pain management than targeting only one site and is the underlying principle of treating pain in a multimodal fashion.

Multimodal pain management

In multimodal pain management, nonopioid analgesics are administered with opioids to reduce the cumulative opioid dose administered and thereby reduce opioid-induced side effects, such as nausea, vomiting, respiratory depression, and pruritus (2,3,23,24). Although multimodal analgesia unquestionably reduces opioid analgesic requirements, its efficacy at reducing opioid-induced side effects is not as clear (23,24).

Nonopioid (or 'weaker analgesics with antipyretic activity') analgesics

The nonopioid analgesics comprise the first step in the World Health Organization (WHO) cancer pain ladder treatment guidelines (25). These 'weaker' or 'milder' analgesics with antipyretic activity comprise a heterogeneous group of nonopioid analgesics. The most common are acetaminophen (paracetamol), NSAIDs (ibuprofen, naproxen, ketoprofen, diclofenac), and the selective cyclooxygenase (COX-2) inhibitors (celecoxib) (Table 1) (26). They produce various degrees of analgesia, antiinflammatory, antiplatelet, and antipyretic effects primarily by blocking peripheral and central prostaglandin and thromboxane production by inhibiting cyclooxygenase types 1, 2, and 3. These metabolites of cyclooxygenase sensitize peripheral nerve endings and vasodilate blood vessels causing pain, erythema, and inflammation. Alternatively, acetaminophen may exert its analgesic (and probably antipyretic) effects by its degradation into an anandamide (an

endocannabinoid) reuptake inhibitor (AM404) within the body, thus classifying it as prodrug or an indirect cannabimimetic (27).

These analgesic agents are usually administered enterally or, on occasion, the rectal route and are particularly useful for inflammatory, bony, or rheumatic pain. Parenterally administered agents, such as ketorolac and acetaminophen, are available for use in children in whom the oral or rectal routes of administration are not possible (28,29). Unfortunately, regardless of dose, the nonopioid analgesics are limited by a 'ceiling effect' above which pain cannot be relieved by these drugs alone. Because of this, these weaker analgesics are often administered in oral combination forms with opioids such as codeine, oxycodone, or hydrocodone. Although the concept is good, it is better to prescribe the drugs individually rather than single combination products to prevent inadvertent acetaminophen-induced liver toxicity (30).

Only a few trials have compared the efficacy of these drugs in head-to-head competition, and, in general, these studies have shown that there are no major differences in their analgesic effects when appropriate doses of each drug are used. The commonly used classic NSAIDs have reversible antiplatelet adhesion and aggregation effects, which are attributable to the inhibition of thromboxane synthesis (31,32). As a result, bleeding times are usually slightly increased but, in most instances, they remain within normal limits in children with normal coagulation systems. Nevertheless, this side effect is of such great concern, particularly in surgical procedures in which even a small amount of bleeding can be catastrophic such as neurosurgery, that few clinicians prescribe them in the immediate postoperative period even though the evidence supporting increased bleeding is equivocal at best.

Acetaminophen (paracetamol)

One of the most commonly used nonopioid analgesics in pediatric practice remains acetaminophen, although its analgesic effectiveness in the neonate is only now becoming clear (29,33,34). Unlike aspirin and other NSAIDs, acetaminophen produces analgesia centrally as a COX-3 inhibitor and via activation of descending serotonergic pathways (35). It is also thought to produce analgesia as a cannabinoid agonist and by antagonizing NMDA and substance P in the spinal cord (36). Acetaminophen is an antipyretic analgesic with minimal, if any, antiinflammatory and antiplatelet activities and takes about 30 min to provide effective analgesia. When administered orally in standard doses, 10–15 mg·kg⁻¹, it is extremely safe, effective, and has very few serious side effects. When administered rectally,

Table 1 Nonopioid analgesics

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

^aSafety of nonsteroidal antiinflammatory drugs (NSAIDs) such as ketorolac or ibuprofen in children less than 3–6 months of age is not well established.

higher doses, 25–40 mg·kg⁻¹, are required (37,38). An intravenous formulation is now available and can be used in patients in whom the enteral route is unavailable (29). Finally, to prevent fulminant hepatic necrosis, the daily maximum acetaminophen dose, regardless of formulation or route of delivery, in the preterm, term, and older child is 60, 80, and 90 mg·kg⁻¹, respectively (39,40).

Opioids

Over the past forty years, multiple opioid receptors and subtypes have been identified and classified. There are three primary opioid receptor types, designated mu (µ) (for morphine), kappa (κ), and delta (δ). These receptors are primarily located in the brain and spinal cord, but

also exist peripherally on peripheral nerve cells, immune cells, and other cells (e.g., oocytes) (41,42). The mu receptor is further subdivided into several subtypes such as the mu1 (supraspinal analgesia), mu2 (respiratory depression, inhibition of gastrointestinal motility), and mu3 (antiinflammation, leukocytes), which affects the pharmacologic profiles of different opioids (43,44). Both endogenous and exogenous agonists and antagonists bind to various opioid receptors.

Following surgery, which opioid to prescribe, how it should be administered, at what dose, and by which route is parochial and based on institutional and practitioner preference (Table 2) (45,46). In the immediate postoperative period, intravenous morphine, fentanyl, or hydromorphone are the most commonly prescribed opioid analgesics. These potent

Table 2 Opioid analgesics

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

^aDue 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).

^bMeperidine is metabolized to normeperidine which can cause seizures.

analgesics are usually given either by a nurse at scheduled time intervals (e.g., every 4 h) or on an as-needed basis *pro re nata* (PRN), or by the patient (or surrogate, the parent or the bedside nurse) using a patient-controlled analgesia (PCA) pump.¹ Occasionally, opioids are given by continuous infusions with breakthrough dosing (administered by the nurse PRN or by the patient using a PCA trigger device) for episodic pain. All are effective, and which technique may be better or safer has never been adequately investigated.

Finally, once bowel function returns, usually within 1–3 days of the surgical procedure, patients are transitioned to oral opioids given either alone or combined with acetaminophen. The predominant oral opioid currently used is oxycodone and not codeine.¹ Oxycodone has supplanted codeine in current pediatric pain practice, because oxycodone, unlike codeine, is not a pro-drug and does not require the cytochrome P450 2D6 isoenzyme to metabolize codeine into its active morphine form (47–49). A small number of patients are

either slow or rapid metabolizers, which can result in either too little or excessive morphine production. Although the former would result in pain, the latter could result in catastrophic respiratory depression. To minimize these risks, oxycodone has supplanted codeine as the preferred oral opioid in the United States, even though it is not labeled by the United States Food and Drug Administration for use in pediatric patients. This underscores the urgent need for pediatric labeling to guide practitioners (50).

Side effects of opioids

Common side effects of opioids include nausea and/or vomiting, sedation, pruritus, miosis, constipation, urinary retention, and the development of drug tolerance and dependence. Respiratory depression is the most feared side effect but is fortunately very rare. On the other hand, constipation occurs universally in all patients receiving opioids and underscores the need for a bowel regimen (e.g., dietary fiber or polyethylene

Table 3 Common drugs for treatment of opioid-induced side effects

Side effect	Drug	Starting doses and intervals	
		<50 kg (mg·kg ⁻¹)	>50 kg and adult (mg flat dose)
Constipation	Senna PO only	10 mg·kg ⁻¹ Q bedtime	187–364 mg Q bedtime
Constipation	Docusate PO only	10 mg·kg ⁻¹ Q 4 h	50–500 mg In 1–4 doses Not to exceed 500 mg per day
Nausea	Serotonin receptor antagonists IV only	Ondansetron 0.15 mg·kg ⁻¹ Q 6 h Dolasetron 0.35 mg·kg ⁻¹ Q 6 h	4 mg Q 6 h 12.5 mg Q 6 h
Nausea and itching	Diphenhydramine IV or PO	0.5–1 mg·kg ⁻¹ Q 4–6 h Can be sedating	25–50 mg Q 4–6 h Can be sedating
Itching	Hydroxyzine PO only	0.25–0.5 mg·kg ⁻¹ Q 6 h Not more than 50 mg per day Can be sedating	25 mg Q 6–8 h

glycol) whenever opioids are prescribed. Some common side effects, particularly itching, nausea, and/or vomiting, can be maddening and worse than the pain for which the opioids are being prescribed. Indeed, many patients would rather have pain than experiencing these side effects. Finally, itching is usually worse with parenteral or spinal (epidural or intrathecal) opioid administration. Unfortunately, it is beyond the scope of this article to discuss the management of opioid-induced side effects or prevention in detail (Table 3), but a novel approach used extensively in our practice is to utilize low-dose naloxone infusions (0.25–1.5 µg·kg⁻¹·h⁻¹). These infusions have been shown to be effective prophylactically at preventing many opioid-induced side effects, particularly pruritus, in patients treated with continuous opioid infusions (51–53). Finally, there is an increasing push by safety advocates to utilize respiratory monitoring, such as capnography, inductance plethysmography, and adhesive sensors with integrated acoustic transducers in patients treated with continuous opioid infusions

or with PCA (54,55). The utility and ability of pediatric patients to tolerate many of these monitors is unknown.

Analgesic adjuvants

Adjuvant pain medications are drugs whose primary indication is not to treat pain, but that may have analgesic properties in specific circumstances. Many of the drugs which will be discussed below were initially used to treat neuropathic and chronic pain, but are now increasingly being used to treat acute pain as a part of a multimodal therapeutic regimen.

Local anesthetics and neural blockade

Sensation to the muscles which attach to the skull, the scalp, the periosteum, and to some extent the dura is provided by all three divisions of the trigeminal nerve and the ventral rami of the 2nd and 3rd cervical nerve roots (Figure 2) (17). The ophthalmic branch of the trigeminal nerve gives rise to the supraorbital and supratrochlear nerves, the maxillary division gives rise to the zygomaticotemporal nerve, and the posterior trunk of the mandibular division gives rise to the auriculotemporal nerve. The lesser occipital nerve originates from the ventral ramus of the 2nd cervical nerve root, whereas the greater occipital nerve originates from the ventral rami of the 2nd and 3rd cervical nerve roots. All of these nerves are readily accessible for neural blockade (Figure 2) (17).

Local anesthetics are drugs that reversibly block conduction of neural impulses along central and peripheral nerve pathways by plugging the Na⁺ channel and preventing ions from passing, and/or by interfering with conformational changes that allow the Na⁺ channel to open (56,57). By being physically deposited at sites of injury or along nerve pathways or near the spinal cord (Figure 1), local anesthetics block impulse conduction through the inhibition of voltage-gated Na⁺ channels and thereby prevent the achievement of a threshold potential that is necessary for generation of an action potential. In the neurosurgical patient, local anesthetic wound infiltration, as well as specific neural (scalp) blockade, can provide sensory analgesia and dramatically diminish the need for opioids in the immediate postoperative setting (17,58,59). Local anesthetics can be used for most incision wounds, including craniotomy and implantable device battery generator pockets. The most common local anesthetics used for wound infiltration are lidocaine, which should not exceed a dose of

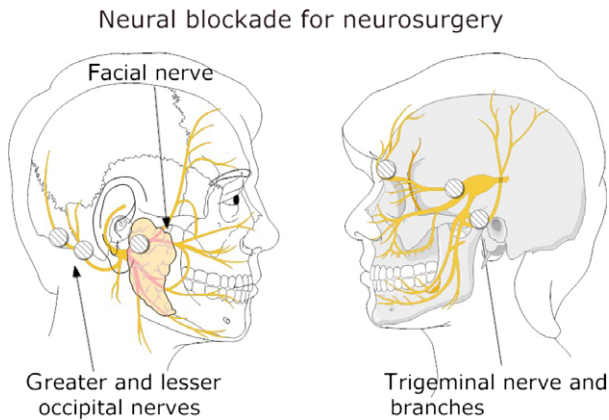


Figure 2 Sensation is provided by all three divisions of the trigeminal nerve (right) and the ventral rami of the 2nd and 3rd cervical nerve roots (left). The ophthalmic branch of the trigeminal nerve gives rise to the supraorbital and supratrochlear nerves, the maxillary division gives rise to the zygomaticotemporal nerve, and the posterior trunk of the mandibular division gives rise to the auriculotemporal nerve. The lesser occipital nerve originates from the ventral ramus of the 2nd cervical nerve root, whereas the greater occipital nerve originates from the ventral rami of the 2nd and 3rd cervical nerve roots. Local anesthetic is injected subcutaneously in areas indicated by the hatched circles. In addition to blockade of the nerves supplying sensation to the surgical site, local anesthetic blockade of the pin sites not otherwise contained by prior nerve blocks should be performed. Local anesthetic administration in the temporal region close to the zygoma can also produce either a deliberate or an inadvertent block of branches of the facial nerve (left), and this should be considered in the postoperative neurologic assessment. This figure was drawn using SmartDraw software, 2014 Enterprise edition).

5 mg·kg⁻¹, bupivacaine, and ropivacaine which should not exceed a dose of 2.5 mg·kg⁻¹. Epinephrine is often added to these local anesthetics to provide vasoconstriction and to potentially extend the duration of the neural blockade.

Corticosteroids

Most patients presenting for craniotomy receive corticosteroids prior to surgery primarily to reduce vasogenic edema. Concurrently, the potent antiinflammatory effects of corticosteroids modulate peripheral nociception (60). Corticosteroids may also alleviate postoperative headache by reducing the chemical meningitis caused by surgical bone dust formation. Even a single dose of a preoperative steroid has been shown to reduce postoperative pain (61). Furthermore, the perioperative administration of corticosteroids may provide enough central antiemetic activity to enable patients to tolerate higher amounts of opioids and achieve better pain control (62). Postoperatively, patients often remain on high

'neurosurgical doses' of steroids, which may produce enough euphoria and analgesia to perpetuate the anecdotal myth of painless neurosurgery.

Anticonvulsants

Gabapentin and pregabalin are the most commonly used anticonvulsants in pain management. They have been most widely studied and used for the treatment of chronic pain in adults with conditions such as postherpetic neuralgia, diabetic neuropathy, and complex regional pain syndromes. Interestingly, despite their names, gabapentin and pregabalin are not GABA minergic and produce analgesia by binding at voltage-gated calcium channel alpha-2 delta (Ca_v-α₂-δ) proteins in the spinal cord and central nervous system (63). Increasingly, they are being used in the perioperative period in adults as a component of multimodal pain therapy but with inconsistent results (64–67). The main side effect of both drugs is somnolence limiting their use in neurosurgical patients. There have been few pediatric studies; in one, adolescent patients who received oral gabapentin before undergoing scoliosis surgery received less morphine postoperatively. However, this reduction in morphine consumption did not reduce opioid-related side effects (68).

Alpha-2 adrenergic agonists

Norepinephrine is involved in the control of pain by modulating pain-related responses through various pathways. Alpha-2 adrenergic agonists, such as clonidine, tizanidine, and dexmedetomidine, have well-established analgesic and sedative profiles and wide application in perioperative multimodal pain management. Clonidine is the prototype and most widely studied of this class of drugs. It can be administered via the epidural, intravenous, subcutaneous, oral, and transdermal routes. Clonidine is traditionally used as an antihypertensive and to minimize the symptoms of opioid withdrawal (69). However, when administered orally, intravenously, or transdermally, clonidine may reduce opioid requirements and improve analgesia. Similarly, the addition of clonidine to local anesthetic solutions for neuraxial or peripheral nerve blockade may enhance and prolong analgesia. However, the analgesic benefits of clonidine remain controversial. Finally, clonidine can be a useful antineuropathic agent, especially in children who cannot tolerate oral medications or who have coexisting problems like steroid-induced hypertension (70). Clonidine use is limited by its side effects, which include bradycardia, hypotension, and excessive sedation.

N-methyl-D-aspartate receptor antagonists

N-methyl-D-aspartate receptor antagonists, such as ketamine and methadone, are important modulators of chronic pain and have been shown in some studies to be useful in preventive analgesia by reducing acute postoperative pain, analgesic consumption, or both when they are added to more conventional means of providing analgesia, such as opioids and NSAIDs, in the perioperative period (71). NMDA receptor antagonists may reduce pain by two nonmutually exclusive mechanisms: a reduction in central hypersensitivity and a reduction in opioid tolerance. Nevertheless, the effectiveness of NMDA antagonists in preventive analgesia has been equivocal at best (71–73). Ketamine is well known as a dissociative general anesthetic and may be an effective adjuvant in pain management when used in low doses (0.05–0.2 mg·kg⁻¹·h⁻¹) (74). We cannot, however, recommend it in neurosurgical patients because of its psychotropic effects. Methadone, on the other hand, can play an important role in multimodal analgesia, both as an opioid and as an NMDA receptor antagonist. It produces long-lasting analgesia and may limit the development of tolerance. Methadone does affect the Q-T interval, and electrocardiographic monitoring may be indicated with initiation and long-term use of the drug.

Muscle relaxants

Muscle relaxants are divided into two groups: neuromuscular blockers and spasmolytic. In reference to pain management, the focus is on spasmolytics, which are centrally acting and help to relieve spasms and musculoskeletal pain. These medications also confer an element of sedation, which may be beneficial in the immediate postoperative period, but are undesirable once a patient seeks to return to normal daily activities or in the postneurosurgical patient. The most commonly used muscle relaxants are the benzodiazepines, such as diazepam and lorazepam.

Others include baclofen, cyclobenzaprine, and tizanidine. Muscle relaxants are beneficial in postoperative analgesia and help to alleviate painful muscle spasms that are not relieved with opioids. By adding spasmolytics to a pain regimen, opioid consumption may be drastically reduced.

Conclusion

Despite the fact that moderate-to-severe pain is common following neurosurgery, pain management has been limited by a concern that opioids, the analgesics most commonly prescribed for pain of this intensity, will adversely affect postoperative outcome and interfere with the neurologic examination. To minimize these and other opioid-induced side effects, we have highlighted some of the drugs and drug families used in multimodal pain management. This analgesic method minimizes opioid-induced adverse side effects by maximizing pain control with smaller doses of opioids supplemented with nonopioid analgesics, such as NSAIDs, local anesthetics, N-methyl-D-aspartate (NMDA) antagonists, α_2 -adrenergic agonists, and anticonvulsants (gabapentin and pregabalin).

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Conflicts of interest

Joanne E. Shay, Deepa Kattail and Athir Morad: None. Myron Yaster: Over the past 5 years, Dr. Yaster has been a consultant for, served on DSMBs, and/or has been involved in industry-sponsored trials for the following pharmaceutical companies: Endo Pharmaceuticals (oxymorphone), Purdue Pharma (oxycodone, hydrocodone), Cadence Pharmaceuticals (IV acetaminophen), and Astra Zeneca.

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