CHAPTER 12

Posttraumatic Pain Management

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EPIDEMIOLOGY

Given the fact that trauma is the precipitating event for a traumatic brain injury (TBI), it is not surprising that pain is one of the most common complaints after TBI. Many patients with TBI's sustain injuries to other parts of their body as well as the head. Although the term "polytrauma" has gained greater recognition in the military setting, this concept is important when considering painful conditions that arise in the general TBI population as well. Studies on the prevalence of pain acutely are complicated by the difficulty that some patients may have in reporting pain because of their clinical and/or cognitive status. Some studies have examined the prevalence of pain more chronically. Nampiaparampil performed a systematic review on the prevalence of chronic pain after TBI and noted headaches in 58% of all patients and chronic pain in 75% of patients with mild TBI and 32% of patients with moderate or severe TBI.[1] This somewhat surprising finding regarding the relationship between TBI severity and pain complaints has also been reported in some studies that have evaluated the prevalence of posttraumatic headaches (PTH),[2] but not others.[3]

Another systematic review was performed by Dobscha and colleagues to better understand the relationship between polytrauma with TBI and pain. Although the results were limited because of a lack of high-quality studies, an association between pain and psychologic factors was noted.[4] This underscores the multidimensional nature of pain in this context. They also attempted to identify reliable assessment tools of pain and functional limitations related to pain but were not able to do so. Using serial interviews at 3, 6, and 12 months postinjury, the incidence of PTH in the first year after TBI in a moderate to severe TBI population was reported as 71%, although for individuals the complaints did not always persist throughout the period studied.[3]

PATHOPHYSIOLOGY

The sensation of pain and its intensity begins with the peripheral receptors (nociceptors) that are activated by thermal, mechanical, and chemical stimuli. Nociceptors are found in the skin, muscle and viscera. They are connected to primary afferent neurons, which represent the first-order neurons in the pain system. These primary afferents consist of A-δ-fibers and C-fibers. A-δ-fibers are myelinated, thin neurons that are 1–5 μm in diameter with small receptive fields that have conduction velocities of 5–30 m/s. Pain from A-δ-fibers comes from thermoreceptors and mechanoreceptors. It is perceived as fast, sharp, well localized, and well defined. C-fibers are small unmyelinated fibers 0.25–1.5 μm in diameter with conduction velocities of 0.5–2 m/s. Pain from C-fibers comes from thermoreceptors, mechanoreceptors, and chemoreceptors. It is perceived as slow, diffuse, poorly localized, burning, or throbbing.[5]

These peripheral first-order afferents have cell bodies in the dorsal root ganglia and enter the spinal cord via the dorsal horn. From here, two distinct and conceptually important pain pathways diverge into the direct and indirect pathways. The direct pathway is also called the lateral pathway or neospinothalamic tract. The direct pathway is of critical importance in acute pain, as it conveys information detailing the type of pain and its location from the nociceptors.[6] In the direct pathway, the first-order neurons entering the spinal cord via the dorsal horn form their first synapse in the nucleus proprius. From the nucleus proprius, these second-order neurons ascend between 1 and 3 levels and then cross via the anterior white commissure to the contralateral side of the spinal cord and become the spinothalamic tract. The spinothalamic tract ascends and synapses at the ventroposterolateral (VPL) nucleus of the thalamus. From the VPL, third-order neurons project to the primary somatosensory cortex of parietal lobe.[7]

The indirect pathway is also called the medial pathway. The paleospinothalamic, spinomesencephalic, and spinoreticular tracts make up the indirect pathway. The indirect pathway is of critical importance in chronic pain and in the mediation of the autonomic, endocrine, arousal, and affective response to pain. The indirect pain pathway also begins centrally at the level of the second-order neurons in the dorsal horn.[6] The paleospinothalamic tract ascends from the dorsal

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horn bilaterally in the ventrolateral spinal cord to its synapses in reticular formation and the intralaminar and midline nuclei of the thalamus. It then projects throughout the limbic system, including the anterior cingulate gyrus. The spinomesencephalic tract projects to the midbrain periaqueductal gray. Like the paleospinothalamic tract, it also synapses on the midline and intralaminar nuclei of the thalamus. Its projections are then distributed broadly to the limbic system and throughout the cortex. The spinoreticular tract travels in the anterior white matter of the spinal cord and terminates in the medullary pontine reticular formation and then onto the midline and intralaminar nuclei of the thalamus. It also projects broadly into the cortex and limbic system.[6,7] Projections of the indirect pathway to the reticular formation are responsible for the arousal aspects of pain. The widespread projections to the limbic system and anterior cingulate gyrus are responsible for the affective and motivational aspects of pain. The periaqueductal gray plays an important role as an antinociceptive center. It stimulates the surrounding brainstem structures to decrease pain via descending inhibitory signals to the dorsal horn cells.[8]

Pain pathways for the head and face are anatomically separate from those for the rest of the body. The trigeminal sensory system provides sensation for the face and the front of the scalp. The upper three cervical dorsal roots carry sensory afferents from the upper neck and posterior scalp. The primary nociceptive afferents from the meninges are carried via the ophthalmic division of cranial nerve V. The brain parenchyma itself has no nociceptive afferents. The ear and external auditory canal have sensory afferents carried by cranial nerves IX and X. Primary nociceptive afferents from cranial nerves V, IX, and X travel to the spinal tract and the trigeminal nerve nucleus.[9]

Peripheral and central pain pathways can become sensitized to painful stimuli, which results in hyperresponsiveness to stimuli or spontaneous discharges in the absence of stimuli.[10] Peripheral sensitization can occur by local inflammatory processes and mediators released during injury that can lower the activation threshold for primary nociceptive afferents. Mediators of the inflammatory response such as cytokines, prostaglandins, and leukotrienes also increase the sensitivity of the nociceptors. Substances such as bradykinin, substance P, serotonin, and histamine are released directly from the nociceptors and also increase their sensitivity.[11] Peripheral sensitization can also occur via the process of windup. In windup, sensitization occurs as the activated C-fiber-evoked responses in the dorsal horn become progressively larger in magnitude. This process stops in the absence of a painful stimulus. Central sensitization involves increased excitability of dorsal horn neurons due to lowered activation thresholds and increased spontaneous activity. Additionally, the receptive field for dorsal horn neurons can expand, further contributing to central sensitization. These processes result in hyperalgesia and allodynia.[12]

ASSESSMENT OF PAIN

Assessment of pain in the patient with brain injury can represent a unique challenge. Altered levels of arousal and memory can interfere with patients' ability to reliably report their subjective experience of pain. For patients who are accurate and reliable historians, standard pain interview questions are appropriate. Assessment of the time of onset, location, intensity, duration, frequency, character, and exacerbating and alleviating factors is advised. It is also useful to inquire about how significantly the pain interferes with day to day activity. Objective rating scales that can be used by reliable patients include the visual analog scale (VAS), the verbal analog scale, the numeric rating scale (NRS), and the picture or faces pain scale. All these scales are easily administered in the clinical setting. The VAS is a 10-cm line with one end representing no pain and the other end representing extreme pain. Patients are asked to place a mark along the line representing the level of their pain. The VAS has shown good validity and reliability in acute[13] and chronic pain.[14] It is useful for measuring change in pain levels in the same patient across different points of time and after specific interventions. The verbal analog scale or verbal rating scale uses a list of adjectives to describe the level of pain intensity. Verbal rating scales have been found to be valid measures of pain and are also sensitive to pain treatments.[15,16] Patients must be literate and familiar with the adjectives used on the scale. Some patients may become frustrated if the best word to describe their pain is not included in the list of adjectives on the scale. The NRS uses a range of digits (for example, 0–10 or 0–100) to rate pain intensity. These tests are quick and easy to administer and do not require literacy or familiarity with particular adjectives. They have been found to be valid for measuring pain and also show sensitivity to treatments.[17,18] The faces pain scale uses a series of photographs or drawings of faces displaying varying levels of pain and discomfort. Patients choose which face best represents their level of pain. The faces pain scale has been demonstrated to be a valid measure of pain and is also sensitive to treatments. The faces pain scale is particularly useful in children, who

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tend to prefer it, but it is also valid in adults.[19–21] It should be noted that all these scales primarily assess the intensity of pain but do not assess the pain location, affective and behavioral components of pain, or its impact on daily functioning. Pain drawings are effective to measure pain location. The VAS and verbal analog scale can be modified to measure the affective components of pain, and these can be used quickly in the clinical setting. However, they have not been proven to be reliable in truly differentiating the affective component from the pain intensity.[22]

For patients with chronic pain or significant affective or behavioral pain components, longer and more in-depth formal assessments are advised. Referral to specialty pain clinics should be strongly considered for patients with chronic pain and with significant affective symptoms, behavioral changes, and functional deficits related to their pain. A multidisciplinary approach and evaluation should be performed and can include neuropsychologic evaluation. Commonly used assessments such as the McGill Pain Questionnaire, Multidisciplinary Pain Inventory, Short Form-36 Health Survey, Sickness Impact Profile, Beck Depression Inventory, Beck Anxiety Inventory, and Minnesota Multiphasic Personality Inventory are frequently incorporated in a neuropsychologic assessment of pain and aid the clinician in developing a comprehensive picture and treatment plan.[5]

For patients who are unable to accurately respond due to cognitive or communication deficits, there are other options to objectively assess pain. A variety of observational pain scales exist, such as the Faces, Legs, Activity, Cry, Consolability (FLACC) Scale. Like other observational pain scales, the FLACC was designed to objectively measure nonverbal behaviors to assess pain. FLACC was originally developed for infants and preverbal children, but it has been validated for use in adults with cognitive impairment.[5] Measuring pain in patients with disorders of consciousness (DOC) is even more challenging and controversial. One of the central questions in patients with DOC is whether or not they can perceive the subjective experience of pain. To answer this question, one must differentiate between nociception and pain. Nociception involves the basic processing of noxious stimuli. In nociception, peripheral receptors detect tissue damage/injury and carry sensory information via the lateral/direct pain pathway to the primary somatosensory cortex (S1) and secondary somatosensory cortices (S2).[23] Activation of the lateral network is responsible for the sensory discriminative aspects of pain.[24] To experience the subjective sensation of pain, the medial/indirect pathway must be activated. The medial pain pathway involves the cingulate, anterior insula, and prefrontal cortices. The medial pathway is involved in the motivational-affective and cognitive-evaluative aspects of pain processing.[25,26]

Several studies have shown differences in the activation of the medial pathway in patients in the vegetative state compared with patients in the minimally conscious state. Laureys et al. used positron emission tomography (PET) imaging to study brain metabolism in patients with DOC in response to electrical stimulation of the median nerve. Patients in the vegetative state showed severely impaired functional connectivity in the corticocortical pathways connecting the primary somatosensory cortex and the secondary somatosensory cortex compared with healthy controls. They concluded that the impaired connectivity between S1 and higher order associative cortices reduced the likelihood that pain is experienced in an integrated manner in patients in the vegetative state.[27] Conversely, Boly et al. also used PET imaging to evaluate brain activation in patients in the minimally conscious state compared with healthy controls in response to noxious stimuli. They found similar patterns of activation of the medial network in minimal consciousness compared to controls, including activity in the S2, insular cortex, posterior parietal cortex, and anterior cingulate cortex. They concluded that it was likely that minimally conscious patients perceive unpleasant aspects of pain.[28] However, Markl et al. evaluated functional magnetic resonance imaging (MRI) activation triggered by noxious stimuli in 15 patients in the vegetative state due to nontraumatic injury, compared with 15 healthy controls. In their sample, 30% had some degree of activation of the medial pain pathway, including the anterior cingulate cortex and the anterior insular cortex. Although activation and connectivity was reduced in the vegetative group, there still exists the possibility of processing the affective-emotional components of pain to some level.[29]

The Nociceptive Coma Scale (NCS) is an observational pain assessment tool developed with the specific purpose of assessing nociception in patients with DOC. The initial version was composed of four subscales assessing motor, verbal, and visual responses to noxious stimuli.[30] In a study of 40 patients with DOC, the NCS was found to be have good interrater reliability and good concurrent validity compared with the FLACC scale, Neonatal Infant Pain Scale, the Pain Assessment in Advanced Dementia Scale, and the Checklist of Nonverbal Pain Indicators. Additionally, it had greater sensitivity and broader score range than those measures, with lower scores for patients in the

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vegetative state compared with those who were minimally conscious.[31] The NCS was revised into the NCS Revised (which no longer included a visual response subscore) after a follow-up study of 64 patients with DOC showed no differences in the visual subscale score between noxious and nonnoxious stimulation.[32]

PAINFUL CONDITIONS

Painful Orthopedic and Musculoskeletal Conditions

Extremity fractures are common in TBI and are frequently a source of pain. Extremity injuries occur in as many as 60% of patients with head injury.[33] Although most bony injuries are diagnosed on an initial skeletal survey when a patient presents emergently for care, sometimes complete orthopedic evaluation is delayed due to the need to treat life-threatening injuries. Additionally, comatose or confused patients are unable to accurately communicate regarding areas of pain or tenderness, which require further evaluation.[34] It is estimated that up to 10% of orthopedic injuries will be missed initially.[35] For these reasons, clinicians working with patients with TBI need to have a high index of suspicion for missed fractures and orthopedic injuries. Extremity fractures are sources of pain in themselves, but they also increase the risk of developing several other painful conditions. Internal rotation contractures and adhesive capsulitis are common complications following shoulder girdle fracture. The bones of the shoulder girdle are the most commonly injured upper limb bones in patients with TBI. Injuries commonly occur to the acromioclavicular joint, clavicle or sternoclavicular joint. Therapeutic range of motion exercises should be started as soon as medically possible following shoulder girdle fractures. Brachial plexus injuries are also potentially painful conditions and are common after shoulder girdle fractures. Radial nerve injury should be suspected in all cases of humeral fracture. Elbow fractures are associated with ulnar nerve injury and heterotopic ossification (HO).[34] HO is seen in greater than 60% of operatively managed acetabular fractures.[36]

Once a fracture is identified, it is critical for the treating rehabilitation team to be confident that proper orthopedic care has been instituted to minimize the pain and risk for further fracture-related complications such as hardware failure, displacement, or nonunion. Kushwaha and Garland advocate for early surgical treatment of patients with extremity fractures once intracranial edema has reached the peak level and has begun to subside at approximately 7–10 days postinjury.[34] Proper orthopedic care also involves clear guidelines on the weight-bearing status, range of motion restrictions, and the method of application of long braces and splints. Modalities should be strongly considered to reduce pain from fractures. The authors suggest cryotherapy in particular because of its role in reducing inflammation and pain. We also advocate for the use of a stepwise approach of pharmacologic treatment of fracture pain starting with nonnarcotic medications. Acetaminophen is a good first-line choice given its favorable side effect profile and analgesic properties. Nonsteroidal antiinflammatory medications (NSAIDs) can be added if acetaminophen is ineffective. If pain remains problematic and is interfering with progress in rehabilitation or causing significant distress, then opiate narcotics should be considered. Adjunctive pain control can be attempted with medications such as gabapentin and pregabalin, both of which have been shown to improve pain control while decreasing opiate requirements.[37] The use of topical lidocaine patches is of questionable value in terms of analgesic effect and decreasing opiate requirements.[38]

Painful contractures are another potential pain generator for patients with TBI. Painful contractures can come from a variety of different mechanisms. They may arise from severe spasticity with progressive loss of range of motion, reduced mobility due to pain, progressive bone formation from HO, or prolonged positioning due to weakness. The reader is referred to the chapter on spasticity for treatment of contractures related to spasticity and treatment of painful muscle spasms. Commonly used spasmolytic medications are listed in Table 12.1. The best approach for painful contractures is to prevent them from occurring. Mobilization and rehabilitation efforts should start as soon as possible and continue through the full course of recovery. Early mobilization in the neurologic intensive care setting has been shown to be safe and effective at improving mobility.[39]

Hemiplegic shoulder pain is common in patients with TBI and stroke. Prevalence of shoulder pain in TBI is estimated to range between 4% and 24%.[40] One series of patients with TBI admitted to an acute inpatient rehabilitation unit found the prevalence of hemiplegic shoulder pain to be 62%.[41] The differential diagnosis of the painful hemiplegic shoulder is broad and includes fractures, spasticity, deep vein thrombosis, peripheral nerve injury (including plexopathy), complex regional pain syndrome (CRPS), rotator cuff injury, painful subluxation, central pain syndrome, and HO. The most important step in treating the painful hemiplegic shoulder is finding the correct diagnosis. In a patient with a painful hemiplegic shoulder, it is suggested that

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TABLE 12.1
Common Medications Used to Address Painful Conditions for Patients After Traumatic Brain Injury

Medication	Primary Mechanisms of Action	Common Side Effects	Metabolism
Acetaminophen	Inhibits prostaglandin synthesis	Nausea, symptoms related to liver toxicity	Liver (multiple CYP isozymes)
NSAIDs	Block release of cyclooxygenase:	Dizziness, nausea, diarrhea, constipation	Liver
Cox-1 (multiple)	Cox-1	Increased risk of GI side effects vs. Cox-2	Multiple CYP isozymes
Cox-2 (celecoxib)	Cox-2	Increased risk of CV side effects versus Cox-1	CYP2C9
Tricyclic antidepressants	Inhibit norepinephrine and serotonin reuptake	Cardiac conduction abnormalities, sedation, anticholinergic (especially tertiary amines), lower seizure threshold	Liver (CYP2D6)
Serotonin norepinephrine reuptake inhibitors	Inhibit serotonin and norepinephrine reuptake	Nausea, somnolence, headache (all); dry mouth and fatigue (duloxetine); insomnia, dizziness, nervousness (venlafaxine)	Liver (CYP2D6, CYP1A2)
ANTICONVULSANTS			
Carbamazepine	Stabilizes neuronal sodium channels	Ataxia, dizziness, nausea, vomiting, SIADH	Liver (CYP3A4)
Gabapentin	Not well defined	Fatigue, somnolence, dizziness	Renal
Pregabalin	Not well defined	Dizziness, somnolence, visual changes, fatigue	Renal
Opioids	Via opiate receptors	Somnolence, constipation, mood disturbances, respiratory depression, abuse risk	Liver (CYP3A)
Triptans	5-HT_{1B} and 5-HT_{1D} receptor agonist leads to intracranial arterial vasoconstriction (some controversy), inhibition of release of substance P, and calcitonin gene–related peptide	Paresthesias, neck tightness, nausea, somnolence, fatigue (relative frequency varies among different triptans)	Liver (MAO-A and CYP1A2)
β-Blockers (propranolol)	β_1 and β_2 receptor blocker	Bradycardia, hypotension, lethargy, fatigue, respiratory distress	Liver (CYP2D6 and CYP1A2)
ANTISPASMODICS			
Dantrolene	Blocks calcium release from sarcoplasmic reticulum	Dizziness, weakness, fatigue, drowsiness, diarrhea, hepatotoxicity	Liver (various microzymes)
Tizanidine	α_2-Agonist	Dizziness, dry mouth, hypotension, somnolence, hepatotoxicity	Liver (CYP1A2)
Baclofen	$GABA_B$ agonist to increase inhibitory signals to dampen spinal reflex arc	Somnolence, dizziness, nausea, cognitive deficits	Liver, with the majority excreted unchanged by kidney

5-HT, 5-hydroxytryptamine; *Cox-1*, cyclooxygenase-1; *Cox-2*, cyclooxygenase-2; *CV*, cardiovascular; *CYP*, cytochrome P450; *GABA*, γ-aminobutyric acid; *GI*, gastrointestinal; *MAO*, monoamine oxidase; *NSAIDs*, nonsteroidal antiinflammatory drugs; *SIADH*, syndrome of inappropriate antidiuretic hormone.

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one start by generating a differential diagnosis based on knowledge of the mechanism of injury (i.e., TBI vs. non-TBI vs. stroke). For instance, fractures, peripheral nerve injuries, brachial plexopathies, and rotator cuff tears are much more likely in traumatic injuries than in nontraumatic injuries. Taking a careful pain history will help to narrow down the differential further, provided the patient is able to communicate effectively. Next, observation and visual inspection is important to look for signs of swelling, warmth, discoloration, skin changes, obvious bony deformity, or subluxation. This can be followed by physical examination looking for the presence of allodynia or hyperpathia. Examination of active and passive range of motion should ensue, with careful attention being paid to the degree of spasticity and loss of range of motion with external rotation and abduction. Further imaging with x-ray, venous Doppler ultrasound, MRI, electromyography/nerve conduction studies. or triple phase bone scan may be required for diagnosis of fractures, deep vein thrombosis, rotator cuff injury, peripheral nerve injury, or CRPS, respectively.

Heterotopic Ossification

HO is the formation of abnormal, ectopic bone containing bone marrow inside soft tissues. It can be seen following peripheral trauma (fractures, dislocations, burns, and postsurgery) and central nervous system (CNS) injury, such as stroke, TBI, or cerebral anoxia. When HO follows CNS injury, it is referred to as neurologic heterotopic ossification (NHO).[42] Although estimates of the incidence of HO can vary widely, from as low as 11% to as high as 76%, the incidence of symptomatic HO is approximately 10% in patients with TBI.[43,44] NHO develops from concomitant injury to the CNS and to peripheral tissues surrounding joints.[45] These injuries stimulate an inflammatory cascade that releases growth factors and cytokines that cause proliferation of fibroblasts and collagen deposition at the peripheral injury site. Sites of peripheral injuries tend to be significantly hypoxic, and this hypoxic environment stimulates the congregation of mesenchymal cells and osteoprogenitor cells, which further differentiate into chondrocytes. The chondrocytes deposit cartilage, and remodeling of the cartilage matrix stimulates angiogenesis. Newly formed blood vessels bring a blood supply, which alters the hypoxic environment and leads to the differentiation of osteoprogenitor cells into osteoblasts. Osteoblasts deposit osteoid on the previous cartilage sites. Mineralization and remodeling of the heterotopic bone into mature lamellar bone with Haversion canals occurs slowly over time.[46] The presence of Haversion canals, blood vessels, and a marrow cavity make HO unique from other conditions causing ectopic bone formation, such as dystrophic calcification.[47]

NHO is considered a painful condition, largely due to the high levels of inflammation found surrounding the affected joints. Clinically, areas of HO are associated with warmth, swelling, erythema, and soft tissue breakdown. Additionally, as more bone is laid down, joint mobility is compromised and can ultimately lead to ankyloses in painful or uncomfortable positions. Overall, 20% of patients with NHO develop painful nerve impingement or entrapment and contractures. The only established treatment for HO is surgical excision.[48] Indications for surgery include nerve or blood vessel entrapment, limited active function (such as actively moving a limb), limited passive function (such as being seated properly or impaired access for hygiene), and pain. Up until recently, HO excision surgery was delayed until the HO matured and was fully formed because of the risk of recurrence. However, new evidence suggests that the rate of HO recurrence is not affected by HO maturity. A survey of 570 patients with NHO who underwent surgical excision was published in 2011.[43] The researchers found that recurrence of NHO postexcision was not associated with the cause of CNS injury (traumatic injury, stroke, or cerebral anoxia), sex, age at the time of injury, presence of multisite NHO, or time from the CNS injury to the time of surgery. In this series, 181 surgeries were performed within the first year without any recurrence of HO through the 6 months follow-up period. Conversely, in 1999, Lazarus et al. studied 24 patients with NHO about the elbow who underwent surgical excision. They found that a long delay before surgery had a negative effect on recovery of range of motion postsurgery.[49] Other concerns with prolonged delay before surgery for an ankylosed joint include bone loss of the articular structure (i.e., femoral head) and increased risk of perioperative fracture.[50] Surgery can be considered once there is clear indication and the patient is medically stable and appropriate for surgery.

No pharmacologic treatment is available to reverse the process of NHO by decreasing the burden of cartilage and bone matrix once it has been laid down. Instead, pharmacologic treatment of NHO is aimed at slowing down the process of laying down new bone. Etidronate is a bisphosphonate that has been shown to prevent HO formation by inhibiting the mineral phase of hydroxyapatite crystals. Etidronate has a role in decreasing inflammation if given intravenously early in the course of HO in patients with spinal cord injury.[51] It may provide some pain relief by blocking

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the inflammation in HO but otherwise is not thought to have significant analgesic effects. The NSAIDs indomethacin and rofecoxib have been used successfully to prevent HO formation following hip surgery and TBI,[52,53] although rofecoxib has been withdrawn from the market because of safety concerns. Unfortunately, there is a paucity of evidence supporting their efficacy in slowing down or halting the process of NHO following TBI once the process has already started. Given the large amount of inflammation described in NHO, NSAIDs are still considered useful agents in treating pain and inflammation. Indomethacin can be prescribed in short-acting formulation at a dose of 25 mg three times per day or in its long-acting formulation at a dose of 75 mg once daily.[52] Potential treatment effects of NSAIDs need to be considered against side effects including increased risk of bleeding, gastritis, impaired bone healing, and renal injury. Impaired bone healing is an important consideration given how commonly fractures co-occur in patients with TBI.

NEUROPATHIC PAIN

Patients with TBI may develop posttraumatic neuropathic pain as a consequence of the underlying primary traumatic injury. Neuropathic pain may result from a number of different lesions and have multiple underlying pathophysiologic mechanisms. Although a comprehensive discussion of this condition is beyond the scope of this chapter, when treating patients with traumatic brain injuries and associated painful conditions it is helpful to have a general understanding of some of the more common neuropathic pain conditions as a starting point for the diagnosis and management of these conditions. For this discussion, neuropathic pain is categorized as peripheral pain, central pain, and CRPS.

Peripheral Neuropathic Pain

Patients who sustain a TBI may also have a number of other associated injuries. Among them are injuries to the peripheral nerves. One study in a general trauma population identified an overall incidence of peripheral nerve injuries of 2.8%. Almost half of these injuries were in patients who were involved in motor vehicle crashes. The radial nerve was the most common upper extremity nerve injury, and the peroneal nerve, the most common lower extremity nerve injury.[54] Although damage to the afferent neuronal pathways is an important component, other mechanisms are also involved, including spontaneous ectopic activity of primary afferent neurons, peripheral sensitization, and central sensitization.[55] Although diagnosis can be challenging when evaluating a patient with cognitive and/or language deficits, characterization of the pain can be helpful. This type of pain is often described as tingling, burning, or shooting. Hypoesthesia, hypoalgesia, hyperalgesia, and allodynia may be present on examination.

Most of the larger randomized controlled trials regarding the pharmacologic treatment of peripheral neuropathic pain have focused on more common conditions such as diabetic neuropathy or postherpetic neuralgia. For these conditions, level A evidence supports the use of tricyclic antidepressants (TCAs), some serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentin, and pregabalin.[56] There is much less evidence regarding neuropathic pain secondary to traumatic nerve injuries, although some evidence exists suggesting that the cause may not be an important factor with regard to pharmacologic efficacy.[57] Gordh and colleagues reported efficacy in some secondary outcome measures of pain in a randomized, double-blind, placebo-controlled study using gabapentin.[58] Ranoux and colleagues demonstrated the efficacy of botulinum toxin A compared with placebo using a numerical pain rating scale as the primary outcome measure.[59]

The evidence supporting nonpharmacologic management of peripheral traumatic neuropathic pain is also limited. In part due to the relatively low risk, transcutaneous electrical nerve stimulation has been employed. Similarly, repetitive transcutaneous magnetic stimulation has also been employed with some weak evidence of efficacy, although results are often short lived. More invasive surgical intervention such as spinal cord stimulation, deep brain stimulation, and motor cortex stimulation, as well as intrathecal drug delivery systems, are also available.

Central Pain

Central pain is pain that is related to a lesion of the CNS. This pain has been studied most closely in patients with stroke and is often referred to as central poststroke pain (CPSP). Some of the other most frequent conditions in which central pain has been studied are spinal cord injury and multiple sclerosis. Another term often encountered is "thalamic syndrome," which highlights the presumed pathophysiologic role of the spinothalamic tract. Lesions involving the spinothalamocortical system result in sensory deficits that may lead to the disinhibition of thalamic nuclei and the evolution of spontaneous pain and/or allodynia.[60] It is likely that central sensitization, as described previously, plays a role in this process. Central pain is often characterized

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as burning, throbbing, tingling, or shooting. It can be spontaneous or evoked. Allodynia and hyperalgesia are often considered to be key components in the diagnosis of CPSP. Information regarding central pain after TBI is limited. Ofek and colleagues performed a study comparing patients with TBI who had chronic pain with a group of patients with TBI who did not report chronic pain and with a group of pain-free volunteers. The group that complained of chronic pain had findings consistent with the characteristics of central pain including allodynia and dysesthesias. This group also had an increase in dysregulation of pain and temperature sensations, with a significant decrease in thermal sensation in the painful regions rather than the pain-free regions. These findings, as well as the described symptoms, support the conclusion that these patients were experiencing central pain.[61]

Information regarding pharmacologic management of central pain is limited to causes other than TBI. A recent systematic review using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) classification system gave strong support for the use of TCAs, SNRIs, pregabalin, and gabapentin.[57] Jungehulsing and colleagues published a double-blind placebo-controlled study of patients with CPSP using levetiracetam, demonstrating that this drug was not effective.[62] Mixed results have been reported using lamotrigine in double-blind, placebo-controlled, crossover studies.[63,64] As will be discussed, the side effect profiles of drugs must be taken into account when choosing an intervention.

Several nonpharmacologic approaches have been studied regarding the management of central pain. Repetitive transcranial magnetic stimulation has been studied with mixed results. Hosomi and colleagues demonstrated a reduction in pain scores for patients with CPSP and demonstrated alterations and cortical excitability for those patients who did respond.[65] A double-blind, placebo-controlled trial by de Oliveira et al. failed to demonstrate improvement in CPSP.[66] More invasive procedures such as motor cortex stimulation have also been utilized with some positive results.

Complex Regional Pain Syndrome

CRPS is a painful condition that may be seen after TBI. One study of 100 consecutive patients who were evaluated upon admission to an inpatient brain injury rehabilitation unit reported a 12% incidence of CRPS diagnosed by triple-phase bone scan. Compared with patients who did not have CRPS, risk factors included associated upper extremity injuries and lower Glasgow Coma Score.[67] Classically, CRPS is divided into two types, with type 1 being defined as having no evidence of nerve damage, whereas type 2 having associated nerve damage. There are several different diagnostic criteria that have been employed, and a number of different diagnostic tests have been proposed. In part, this is likely because the pathophysiology has not been fully characterized. Clinically, in addition to pain the affected limb is often warm, erythematous, and swollen. Over time, the presentation may change to the limb appearing cooler with atrophic skin. Diagnostic testing may include a triple-phase bone scan, with increased uptake in all three phases being considered diagnostic.[68]

Given the lack of a unifying pathophysiologic process, it is not surprising that a number of different interventions have been employed with varying degrees of success. Pharmacologic interventions may include the use of NSAIDs, although there is greater evidence for the use of oral corticosteroids among the antiinflammatory medications. A recent Cochrane review identified weak evidence supporting the use of bisphosphonates and calcitonin, with minimal evidence available to support the use of other oral medications. There was weak evidence that blocking sympathetic nerves with local anesthetics was not effective and that intravenous blockade with guanethidine was not affected by and associated with complications. Daily intravenous ketamine had some support, although complications were also noted with this intervention.[69]

Among nonpharmacologic interventions, there is some evidence that physical and occupational therapy may decrease pain. Management of edema, desensitization, and maintenance of movement and range of motion are also important elements in maintaining function.[70] Mirror therapy has also been demonstrated to be effective in a randomized, sham controlled study of 24 patients with poststroke CRPS 1.[71] Behavioral interventions have also been employed with varying degrees of success.

POSTTRAUMATIC HEADACHES

PTH are defined by the International Classification of Headache Disorders criteria as those that develop within 1 week after head trauma.[72] This is the most common complaint after TBI, with incidence reported as high as 90%. There is some debate as to whether the severity of injury is related to the incidence of PTH.[73] Female gender and a history of headaches before TBI are also risk factors. The pathophysiology of PTH is multifactorial, as is the clinical presentation. Based on the clinical presentation, clinicians often attempt to classify headaches as a way of guiding treatment.

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It should be noted that PTH may present with mixed headache types.

Posttraumatic Migraine Headaches

Migraine headaches have been identified as the most common type of PTH for both mild and more severe injuries. It is typically intense, unilateral, and may be accompanied by complaints of nausea/emesis, visual changes, photophobia, and phonophobia. Patients do not need to have a history of migraines to develop this type of PTH. Pharmacologic management is usually divided into abortive agents (medications that are taken when a headache develops) and prophylactic agents (medications taken to decrease the incidence of headaches). Options for abortive medications include NSAIDs, acetaminophen, opioids, and vasoactive medications such as triptans and ergotamine. Triptans are considered first-line medications for migraine headaches in the general population assuming that there are no medical contraindications. They are effective, and because they are specific to the management of migraines, their efficacy can also be helpful regarding the diagnosis of the type of headache. Use of ergots and acetaminophen also are supported by more than one Class 1 study.[74]

Prophylactic or preventative medications for migraine headache should be considered when there are six or more migraine headache days per month, or a lesser number if the migraine headaches are causing more severe impairment. Increased use of abortive medications may lead to the development of medication overuse headaches or chronic migraines. There are a number of medications that can be used for migraine prophylaxis, including TCAs, calcium channel blockers, β-blockers, and anticonvulsants such as valproic acid and topiramate.[75] When choosing a medication, side effects including, but not limited to, cognitive effects must be considered in the TBI population. When appropriate, nonpharmacologic interventions such as relaxation and behavioral therapy should also be employed. Botulinum toxin is also an effective prophylactic intervention.

Tension-Type Headaches

Tension-type headache is the second most common type of PTH. There is no specific pathophysiologic cause for this headache type. It is often grouped with cervicogenic headaches (headaches with a confirmed cervical source, usually related to cervical vertebral joints and spinal nerves) and myofascial headaches under the category of musculoskeletal PTH. Tension-type headaches are described as mild to moderate in severity, usually bilateral and involving the forehead or temples, and can be described as pressure or bandlike. Nausea and vomiting are not typically seen, and these headaches are often not aggravated by routine physical activity. On examination, trigger points may be identified. These are areas where palpation leads to referred pain in other areas and may reproduce the patient's headache pain. Tenderness in the neck area may indicate increased muscle tension but by itself would not be useful for differentiating tension-type headache from the more narrowly defined cervicogenic headaches.

Tension-type headaches are subdivided as episodic and chronic by the International Headache Society criteria, with chronic being defined as occurring greater than 15 days per month on an average for greater than 3 months while meeting other criteria for tension-type headache.[72] Underlying pathophysiologic processes including chronic peripheral nociceptive sensitivity and stimulation leading to central sensitization likely play a role. Chronic release of pain-related peptides such as bradykinin, prostaglandins, and histamine has also been implicated. Accordingly, initial management aims to decrease pain and inflammation. Antiinflammatory medications and acetaminophen are appropriate initial interventions, and for headaches associated with cervical pain, modalities and physical therapy should be considered unless contraindicated, for example, with neck instability. Studies also support the efficacy of behavioral interventions, which may not be appropriate for a subset of patients with TBI. A multimodal approach based on the management of tension-type headache in the general population should be considered, especially for more chronic cases.[76]

Other Types of Posttraumatic Headaches

Temporomandibular joint dysfunction may be seen after trauma to the head, or may be a preexisting condition exacerbated by trauma. This headache type is typically located in the temporal region and may be exacerbated by chewing. On examination, there is often evidence of an excessive lateral shift, or even clicking or locking when the patient is asked to open and close the mouth. Management may include NSAIDs, changing to softer diets, and the use of oral appliances. Physical therapy may play a role in restoring normal motion, and behavioral and psychologic interventions may also be appropriate as emotional disturbances may worsen the symptoms.[77]

Injury to the head may lead to peripheral nerve injuries. This may be from direct trauma or surgical interventions. This pain is usually described as sharp, shooting or burning. Palpation may lead to identification of the

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area of injury with reproduction of the headache pain. The greater occipital nerve is one of the nerves most commonly injured. The pain is often described as radiating from the back of the head to the periorbital area. This nerve is often injured due to a blow to the back of the head or with whiplash injuries. This headache can be diagnosed by performing a local anesthetic block to the site where pain is reproduced by palpation.[78] This injection may lead to long-term improvement. Medications used for neuropathic pain such as TCAs, SNRIs, and anticonvulsants may also be considered. Other invasive interventions such as radiofrequency ablation have also been employed.

An acute headache, often associated with deterioration in mental status and nausea and vomiting, may be related to increased intracranial pressure. This may be related to a new hemorrhage or acute hydrocephalus. Papilledema is a sign of increased intracranial pressure, and there also may be accompanying focal neurologic changes. Emergent evaluation and management is warranted. Patients may also develop headaches related to low cerebrospinal fluid (CSF) pressure. Patients who have had craniectomies, shunt procedures, or are at risk of CSF leaks may develop these types of headaches. CSF leaks related to head trauma may be identified by clear rhinorrhea or otorrhea. If the patient has had a lumbar puncture, that site should be evaluated for a leak. Treatment is related to identifying the site of the leak. Headache related to craniectomy, that is, the "sunken flap syndrome," often worsens when the patient is upright. Headache may be accompanied by complaints of dizziness or a frank decline in functional status.[79] This condition is managed by cranioplasty unless surgically contraindicated. In cases in which headache is accompanied by fever, nuchal rigidity, and perhaps purulent drainage from a wound site, meningitis or other intracranial infectious process should be immediately ruled out.

Visual deficits are common after TBI, regardless of the severity of injury. These visual deficits may lead to complaints of headache, especially related to visual activities or at times exposure to bright light. A study of combat-injured service members with TBI revealed that almost 50% of participants had convergence insufficiency and accommodative insufficiency. Pursuit and saccadic dysfunctions were noted in 23%, and 87% reported difficulties with reading.[80] Strain with visual activities often leads to headaches described as temporal or "behind the eyes." Management involves identification and treatment of the underlying pathology, and often involves collaboration with specialists in optometry or ophthalmology.

PHARMACOLOGIC CONSIDERATIONS TO TREAT PAIN FOR PATIENTS WITH TRAUMATIC BRAIN INJURY

A number of different pain conditions common in patients with TBI have been described. As part of this discussion, various medications have been identified as being potentially efficacious. However, in the context of rehabilitation of TBI, specific side effects need to be taken into account when making decisions regarding the pharmacologic management of pain. Information regarding specific drugs including their mechanisms of action, metabolism, and relevant side effects are listed in Table 12.1. Many patients are prescribed a number of medications, therefore drug interactions need to be considered, including the effects on metabolism of concomitant medications. General principles regarding pharmacologic management of patients with TBI include minimization of medications and choosing medications that are less likely to interfere with the rehabilitation process. As part of minimizing the overall number of medications, it may be possible to choose a medication that addresses more than one problem. For instance, if pain and depression coexist, it may be possible to prescribe one medication to address both problems.

It is worth highlighting some of the more relevant side effects regarding the TBI population. As noted in Table 12.1, many of the medications discussed have sedation or lethargy listed as side effects. These are common findings or complaints after TBI, and are often the limiting factor when balancing pain management with overall function. Note also that the majority of the medications listed are hepatically metabolized. Patients are often on a number of different medications that are metabolized by the liver, so care must be taken to not overburden the hepatic system. Additionally, some drugs may enhance systems that break down medications (e.g., cytochrome P450), resulting in decreased drug activity at a given dosage.

SUMMARY

Painful conditions are a common component of the clinical presentation of patients with TBI. Clinicians need to be aware of the potential pain generators, especially in patients who may not be able to communicate their distress effectively or accurately. Pain may be a means of identifying previously undiagnosed medical problems. Undertreatment of pain can lead to physical and emotional distress, negatively affecting the outcome. However, pain management must be judicious because inappropriate treatment may also lead to unnecessary complications or poorer patient outcomes.

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