Burn Injury Pain: The Continuing Challenge

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Abstract: The development of more effective methods of relieving pain associated with burn injury is a major unmet medical need. Not only is acute burn injury pain a source of immense suffering, but it has been linked to debilitating chronic pain and stress-related disorders. Although pain management guidelines and protocols have been developed and implemented, unrelieved moderate-to-severe pain continues to be reported after burn injury. One reason for this is that the intensity of pain associated with wound care and rehabilitation therapy, the major source of severe pain in this patient population, varies widely over the 3 phases of burn recovery, making it difficult to estimate analgesic requirements. The effects of opioids, the most commonly administered analgesics for burn injury procedural pain, are difficult to gauge over the course of burn recovery because the need for an opioid may change rapidly, resulting in the overmedication or undermedication of burn-injured patients. Understanding the mechanisms that contribute to the intensity and variability of burn injury pain over time is crucial to its proper management. We provide an overview of the types of pain associated with a burn injury, describe how these different types of pain interfere with the phases of burn recovery, and summarize pharmacologic pain management strategies across the continuum of burn care. We conclude with a discussion and suggestions for improvement. Rational management, based on the underlying mechanisms that contribute to the intensity and variability of burn injury pain, is in its infancy. The paucity of information highlights the need for research that explores and advances the identification of mechanisms of acute and chronic burn injury pain.

Perspective: Researchers continue to report that burn pain is undertreated. This review examines burn injury pain management across the phases of burn recovery, emphasizing 3 types of pain that require separate assessment and management. It provides insights and suggestions for future research directions to address this significant clinical problem.

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Key words: Thermal burn, pain management, phases of burn recovery, inflammation, acute and chronic pain mechanisms, science.
review examines burn injury pain and its management across 3 phases of burn recovery (ie, acute, healing, and rehabilitation), emphasizing 3 types of pain that require separate assessment, management, and frequent evaluation. Although the review addresses patients of all ages, from critical care to outpatients, the primary focus is on pharmacologic management of the adult hospitalized patient who is awake and not supported by mechanical ventilation. The review concludes with a discussion, suggestions for improvement, and a call for critically needed science to guide the standard of care as well as the development of new therapeutic approaches.

Significance

Unrelieved burn injury pain is a significant public health problem. In the United States, an estimated 1.25 million individuals sustain a burn injury each year. Of these, between 700,000 and 827,000 seek care at an emergency department, and between 51,000 and 71,000 require hospitalization. Although these figures reflect decreased prevalence as the result of successful burn prevention strategies, they do not reflect the significant increase in patients surviving major burns. Nor do they reveal that the number of patients admitted to burn centers has increased significantly due to the recognition that even smaller burns require specialized care. Yet, burns are one of the most resource-intensive of all health care conditions. Thus, there has been a widespread trend to treat patients with larger and more complex burns on an outpatient basis and to discharge inpatients sooner. Over the past 10 years, the average length of an inpatient stay declined from 13 days to 8 days. This approach means that outpatients experience more severe pain and have pain management needs across all the phases of burn recovery.

Phases of Burn Recovery

Important to a discussion of burn injury pain is an understanding of burn recovery. Burn recovery is frequently divided into 3 phases, based on local and systemic, pathophysiologic responses. The acute phase, also referred to as the emergency or resuscitative phase (due to the need for massive fluid replacement often required to maintain circulating volume), is when initial wound debridement is performed after the patient has been stabilized. The healing phase is characterized by the goal to accomplish healing, which requires a clean wound bed, achieved through frequent dressing changes or surgical intervention. The rehabilitation, or remodeling phase, is the time during which the intense inflammatory response associated with raised, erythematous (reddened) scar tissue subsides and tissue collagenases cease remodeling, resulting in a softer, less erythematous and sometimes flatter scar. The acute phase may be completely bypassed in smaller injuries and typically lasts 2 to 3 days. The length of the healing phase may be weeks or more, and the rehabilitation phase most often takes at least 1 year but sometimes much longer, depending on patient participation in the treatment plan; patient age; location, size, and depth of burn; as well as comorbid or preexisting conditions.

Pain is the most frequent complaint of burn-injured patients. Burns induce mechanical and thermal hyperalgesia in human skin. However, primary mechanical hyperalgesia, induced by mechanical stimulation of the injured site, is the major source of severe pain after a burn injury. In this review, the terms “pain” and “hyperalgesia” refer to primary mechanical hyperalgesia.

Clinical observations suggest that hyperalgesia is likely to be most severe and variable in intensity during the healing phase. The intensity of hyperalgesia cannot be predicted based on factors such as patient age, sex, ethnicity, education, occupation, or socioeconomic status and does not always correlate with the size of the burn.

Burn Injury Pain Assessment

Assessment tools are essential to the diagnosis of underlying burn pain syndromes and the effectiveness of their treatment. In the burn patient population, the most common pain assessment tools are verbal self-report instruments that measure pain intensity, such as the “0 to 10” numeric rating scale. However, visual analog, descriptor (eg, adjective), face, and color scales, are also used. In 1 of the few studies that examined patient preference, burn-injured patients preferred faces and color scales to the more commonly used visual analogue and adjective scales.

Osgood et al introduced the first pediatric burn pain assessment tool: A large thermometer-like numeric rating scale designed with white numbers (0 to 10) on a crimson background. Whereas this and other pediatric pain assessment tools can be used in adults and elderly patients (eg, faces), no pain assessment tool has been validated for use among elderly burn-injured patients. This may be, in part, because pain in older burn-injured patients is only beginning to be described. Osgood et al included the manually marked visual analog scale as part of their tool. Only 1 study has evaluated the manual visual analog scale. However, research in other patient populations has demonstrated that the verbal descriptor scale is best for measuring pain in older adults, including those with mild to moderate cognitive impairment.

When patients are unable to provide a self-report, behavioral observations may be a valid approach. An observational pain scale has been developed for use in burn-injured children. A cautionary note is warranted, however, because significant discordance has been demonstrated between burn nurses’ and burn-injured patients’ pain assessments. For this reason, individuals who are unable to communicate their pain are at greater risk for undertreatment of their pain—an important clinical problem for which excellent clinical practice recommendations have recently been published.

As in other patient populations, the manually marked visual analog scale is preferred for research purposes because its continuous range makes it a sensitive measure-
Types of Burn Injury Pain

Procedural Pain

Procedural pain (eg, primary mechanical hyperalgesia) is the most intense and most likely type of burn injury pain to be undertreated. Patients describe procedural pain as having an intense burning and stinging quality that may continue to a lesser degree but may be accompanied by intermittent sharp pain for minutes to hours after dressing changes and physiotherapy have ended. Wound debridement, dressing changes, and strenuous physical and occupational therapy that require manipulation of already inflamed tissue may contribute to increased pain and inflammation in burn wounds. In addition, dependent positioning of injured extremities (ie, below the level of the heart) can induce excruciating, throbbing pain, thought to be caused by pressure associated with venous distention in inflamed, edematous tissue. These observations are based on clinical experience, however, and require study. Procedural pain is a multidimensional experience that frequently induces significant anxiety and distress. These multidimensional manifestations of the procedural pain experience are critical aspects of this important clinical problem as emphasized in the following section.

Procedural Pain and Associated Anxiety and Distress

New burn care providers sometimes ask if patients “get used to” or habituate to procedural pain. However, clinical observations and research suggest that procedural pain–associated anxiety may increase over time in burn-injured patients. This finding has important implications for clinical care because strong correlations were found between pain, psychological distress, and physical as well as psychological outcomes in burn-injured children and adults. Anxiety and distress, as measured by tension during burn dressing changes, was significantly related to overall and worst pain, whereas amount of analgesics and anxiolytics given, postburn day, and total body surface area were not.

Anxiolytic agents, such as the benzodiazepines (eg, diazepam, lorazepam, and midazolam) are known to reduce pain and anxiety associated with burn dressing changes in burn-injured adults and children. Lorazepam was found to reduce procedural pain ratings in patients who had “high pain” defined as a baseline of 50 or greater on a 0 to 100 mm visual analog scale. However, benzodiazepines have been found to antagonize opioid analgesia in postoperative patients. Moreover, similar to opioids, patients’ responses to benzodiazepines are highly variable. Although some patients may have development of respiratory depression, others, particularly those with a history of alcohol or chemical dependence, may not respond to doses within the recommended safety and efficacy range. Therefore, the administration of benzodiazepines requires increased staffing to provide close monitoring for untoward effects, a standard of care commonly referred to as “conscious sedation.” Because burn care is resource-intensive and insurance and government reimbursements have declined, the use of benzodiazepines that require a conscious sedation protocol has declined in the acute care setting in some burn centers and is impractical in the outpatient setting. Other classes of sedative hypnotics such as ketamine and propofol significantly reduce pain and associated anxiety and distress during burn dressing change procedures, but their use is usually limited to the critical care setting for the same reason.

Pharmacologic agents have also been used to reduce acute stress symptoms in burn-injured children (eg, hyperarousal and intrusive reexperiencing), including imipramine, chloral hydrate, morphine, and resperidone. However, lack of a clearly defined standardized diagnostic criterion for study entry and use of an unvalidated clinical interview to determine improvement or methodological flaws make the results difficult to interpret. Whether decreasing acute stress symptoms in burn-injured patients with pharmacologic agents translates into a decreased prevalence of traumatic stress disorders is unknown and requires further study. One reason for this may be the difficulty to accurately diagnose traumatic stress disorders in patients with burn injuries.

Prevalence rates for traumatic stress disorders associated with burn injury vary substantially across studies, ranging between 11% and 50%. In addition to pain-associated anxiety and distress, factors that contribute to acute and post-traumatic stress disorders after burn injury include female sex, avoidant coping style, location of burn, preburn depression, type and severity of baseline symptoms, personality disorder, history of alcohol and/or chemical dependency, and poor social support. Findings are inconsistent regarding body image after burn injury. Overall, the data suggest that severe
Burns do not necessarily induce physical impairment or poor psychosocial adjustment, particularly in burned children, but size of burn and in-hospital ratings of stress may predict rate and degree of physical and psychological recovery. These results suggest that in addition to aggressive wound closure, interventions that reduce in-hospital distress may accelerate and improve both physical and psychosocial recovery.

Nonpharmacologic adjuncts to reduce pain and associated anxiety and distress include cognitive techniques (eg, distraction and focusing attention), behavioral techniques (eg, classic conditioning, including pairing relaxation with previously conditioned autonomic responses), education and/or preparatory information (eg, enhancing predictability of sensory and procedural components of aversive procedures), hypnotherapeutic techniques (eg, incorporates behavioral and cognitive techniques with introduction of posthypnotic cues for relaxation), and alternative medicine (eg, massage, acupressure). Of these, hypnosis, music, and virtual reality (ie, technologically driven distraction) have been demonstrated to significantly reduce pain and/or associated anxiety and distress when used as an adjunct to opioid analgesics during burn dressing changes. Patterson et al suggested that hypnosis, which appears to be more effective in patients with severe pain caused by motivational factors, and virtual reality may be combined to optimize their beneficial effects. Preliminary findings support this suggestion as well as the increased efficiency with which hypnosis can be administered by eliminating the need for the presence of a trained clinician, an advantage that may help to offset the cost of expensive equipment required to administer “virtual reality hypnosis.”

Nonpharmacologic interventions can also cause harm. Single-session psychological debriefing was found to increase symptoms of post-traumatic stress disorder in burn-injured patients, similar to other patient populations. In addition, combining attention focusing (ie, attending to procedural sensations) with ignoring has been shown to increase symptoms of traumatic stress (eg, intrusion) in burn-injured patients. A group that was taught to use 2 behavioral coping techniques (eg, as opposed to using 1 or the other), including avoidance (eg, ignoring) and approach (eg, focusing attention), during burn dressing changes reported more traumatic stress symptoms than untreated control subjects. Thus, the use of single-session debriefing and combined use of ignoring and focusing attention during burn dressing changes is not empirically justified and may potentially cause harm. Although the theoretical basis and application of nonpharmacologic adjuncts are not within the scope of this review, they are well described by Patterson et al.

**Background Pain**

Burn-injured patients with high anxiety also tend to report more background pain. Similar to procedural pain, wide variability has been documented in the intensity of background pain after burn injury. Back-ground pain is characterized by its prolonged duration, relatively constant nature, and mild to moderate intensity. Burn background pain is typically described as a continuous “burning” or “throbbing” pain that is present when the patient is relatively immobile. Therefore, it is usually best treated with regularly scheduled analgesics that provide a continuous serum therapeutic blood level.

**Breakthrough Pain**

Similar to postoperative patients, patients with burns experience transient worsening of pain most frequently associated with movement that is referred to as breakthrough pain. Burn-injured patients also describe spontaneous components of breakthrough pain. Spontaneous breakthrough pain may be due to changing mechanisms of pain over time as well as inadequate dosing, which occurs when serum blood levels of analgesics drop below what is needed to control background pain. Spontaneous breakthrough pain is commonly reported by patients in qualitative terms such as “stinging,” “pricking,” “shooting,” and “pounding” (unpublished data). Although pain associated with primary mechanical hyperalgesia caused by movement may also be called procedural pain, most burn care providers consider this pain to be a type of breakthrough pain. Mechanical hyperalgesia of this nature is particularly severe after extended periods of immobility in those patients with injuries over joints and/or in whom the extremities are affected.

For optimal analgesia after burn injury, a guiding principle is that each patient requires a separate assessment of procedural, background, and breakthrough pain throughout the rapidly changing course of burn recovery. The next section describes the pain associated with the 3 phases of burn recovery and how these different types of pain may occur in and interfere with each phase.

**Phases of Burn Recovery and Pain Management**

**Acute Phase**

Stabilization of the patient and preservation of function are the primary goals of treatment during the acute phase. Large thermal injuries (>15% total body surface area) evoke profound systemic fluid shifts and physiologic stress responses. This phase may be completely bypassed in the case of smaller burns and varies in length but typically lasts no longer than 3 days. Acute intoxication with alcohol or chemical substances, which may be a precipitant to the burn injury, may initially complicate care of the burn-injured patient and can adversely interact with analgesic and anxiolytic medications.

**Procedural Pain During the Acute Phase**

Procedural pain during the acute phase may range from mild to excruciating. It is critical to aggressively...
manage pain and anxiety for the first dressing change. If the first dressing change evokes extreme anxiety and emotional distress, clinical experience suggests that these responses are likely to increase over time and may lead to long-term pain management problems. Thus, some burn centers provide anxiolytic medication as an adjunct to opioids as a standard of care during this phase unless otherwise contraindicated.

Of note, patients may have progressed to the rehabilitation phase and then return to the healing phase after required surgical procedures. Thus, the phases of burn recovery do not always occur in a stepwise monotonic progression.

**Background Pain During the Acute Phase**

The severity of background pain during the acute phase may also range widely from none to severe. It is often markedly decreased by covering the wound securely with a moist or occlusive dressing, which suggests a contribution from exposure of the wound to air. Because this type of pain is continuous, controlled release or long half-life opioids such as methadone are particularly effective for the management of background pain.

Moreover, methadone is a μ-receptor agonist and an excitatory amino acid N-methyl-D-aspartate (NMDA) receptor antagonist. Thus, it may be of particular benefit to decrease morphine tolerance, which is often associated with enhanced hyperalgesia in the burn-injured patient.

**Breakthrough Pain During the Acute Phase**

During the acute phase, it is not unusual for the burn-injured patient who appears to have good pain control on a stable analgesic regimen to suddenly experience an increase in the severity of their pain, referred to as breakthrough pain. A subtype of breakthrough pain called end-of-dose breakthrough pain may occur toward the end of a dosing interval presumably because opioid levels have declined below a therapeutic level. Shortening the dosing interval is usually recommended under these circumstances. Increasing the dose without shortening the dosing interval may also be effective, but this approach can result in higher than desirable peak serum levels, producing or increasing undesirable side effects.

**Healing Phase**

During the healing stage, the goal is to promote healing, either by removing devitalized tissue from the injured area, using topical enzymatic preparations and frequent dressing changes or by surgical excision and grafting. During the transition from the acute to the healing phase, a determination is made as to whether the patient will require surgery to accomplish wound closure or "to let the wounds heal on their own" with daily wound care. If wounds cannot contract and approximate their edges together, they will form extremely painful, nonhealing ulcers. However, if wounds heal over a joint, since they will shrink by contraction, they may leave the patient with a contracture, limiting range of motion. Thus, stretching injured tissue during physiotherapy, a major source of primary mechanical hyperalgesia, is vital immediately after and over the long course of burn recovery to prevent contractures and to optimize function.

Because of the time it takes to prepare a clean wound bed necessary for epidermal migration to occur deep dermal burns take longer to heal, which extends the period of time the patient endures severe pain. Moreover, wounds that heal slowly are more likely to scar significantly, a phenomenon associated with prolonged inflammation. Since early excision and grafting significantly reduce mortality and morbidity in the burn-injured patient population, the goal is to establish a wound closure treatment plan as soon as possible. That being said, a determination of the depth of tissue damage is difficult, even for the most experienced clinicians. Moreover, inflammatory responses induce changes in the local microcirculation that contribute to further ischemia. Thus, the extent of tissue damage does not evolve completely for several days (eg, 3 days or longer) after burn injury. During this “wait and watch” period, the burn patient often experiences severe pain and anxiety.

**Procedural Pain During the Healing Phase**

Unlike most acute injuries, procedural burn pain may worsen unpredictably over the course of healing, an event that adds to emotional distress in this patient population. This problem is not limited to a particular phase of burn recovery but is a frequent clinical observation during the healing phase. Moreover, the healing phase can last weeks, months, and sometimes even years, during which time the patient must endure repetitive, exquisitely painful, wound care and/or surgical procedures.

Short-acting, potent opioid analgesics timed to act during peak procedure-induced primary mechanical hyperalgesia are most often indicated. In more severe cases, local nerve blocks or general anesthesia may be an option. Local anesthetic blocks have been used surprisingly sparsely in this patient population. One reason may be that as previously mentioned, invasive lines provide a portal of entry for infection in immunocompromised burn-injured patients. In addition, for regional nerve blocks, an acute pain service is usually required to provide the expertise and oversight necessary for this mode of analgesia.

A common clinical observation in patients experiencing postoperative pain after skin grafting procedures is that the split-skin donor site is substantially more painful than the grafted site. Two studies suggest that local anesthetics can be used to decrease donor site pain in the immediate postoperative period. Bupivacaine at a dose of slightly less than 1.9 mg/kg added to intraoperative donor site infiltration solution was found to be safe, as demonstrated by low blood levels and the absence of clinical signs of toxicity, and effective. In contrast, the topical aerosol application of 0.5% bupivacaine was not as effective as 2% lidocaine when applied intraopera-
tively to donor sites before application of an occlusive dressing. In this study, lidocaine produced an analgesic effect that reduced opioid requirements compared with patients who received 0.5% bupivacaine or placebo.

Research has shown topical as well as preemptive injections of lidocaine to be disappointingly ineffective in healthy volunteers undergoing burn injury, consistent with the poor response observed clinically. In vitro studies show that C-fiber nociceptors require a significantly higher dose of lidocaine (0.8 mmol/L) than A-delta fiber nociceptors, which were blocked by as little as 0.2 mmol/L lidocaine. These differential findings suggest that the analgesic effect of lidocaine is dose-dependent, but little is known about topical lidocaine and the peripheral mechanisms of burn injury pain.

Deep wounds that must heal by contraction and then primary closure if necessary require mechanical stimulation (ie, pressurized spray of water, wet to dry dressings, and so forth). These wounds fill in with vascular granulation tissue, which can be exquisitely sensitive to pressure. Topical lidocaine has met with limited success in these types of wounds. In addition, lidocaine requires caution due to the risk of cardiac arrhythmias and seizures associated with systemic absorption. One study suggested that clean vascular wounds with a minimal amount of associated inflammation may be more responsive to the analgesic effects of topical local anesthetics. Of note, a recent study that compared infected and noninfected burn-injured patients showed a significant increase in pain intensity in patients with infection. Burns induce profound inflammation. It is possible that inflammation induces plastic changes in peripheral C-fiber nociceptors, making them less responsive to local anesthetics, but this mechanism has not been studied.

Regional blocks have also been used to relieve donor site pain. A recent randomized, double-blinded study demonstrated efficacy of a continuous fascia iliac compartment block at the thigh donor site. Prolonged, preemptive nerve block reduced primary and secondary hypalgesia over a period of 12 hours after a thermal burn in human volunteers, whereas erythema and blister formation were not significantly affected.

The analgesic effect of topically applied ketamine and the nonsteroidal anti-inflammatory drug ketorolac have also been evaluated in the burn-injured patient population without success. In addition, morphine has been applied topically (eg, formulated with the antimicrobial cream sulfadiazine), resulting in a slight analgesic effect in the experimental group compared with placebo, but the difference was not statistically significant. Subcutaneous local administration of morphine was effective in attenuating pain after an experimental thermal injury, and topical loperamide, a μ-receptor agonist, was effective after a deep burn in rats. Whereas local subcutaneous morphine sulfate injections are not practical, nor would they be well tolerated, in the clinical setting, the topical administration of opioids such as loperamide warrant further study.

### Background Pain in the Healing Phase

Clinical experience suggests that background pain is less intense than either procedural pain or breakthrough pain, but research is needed to better characterize this type of pain and its variability over the healing phase of burn recovery. A common clinical observation during the healing phase is that background pain may increase precipitously just before epithelialization is complete. This increase in pain characteristically occurs with the appearance of epithelial skin “buds,” structures that herald reepithelialization and subsequent wound closure. This period of healing is exquisitely painful, but the pain ceases rapidly as epithelial cells spread out to cover the burn wound. As noted above, regularly scheduled administration of medications that provides continuous therapeutic serum blood levels is optimal for the management of background pain. Several doses (eg, 5) of systemically administered medication are required before a therapeutic serum level is achieved in burn-injured patients. Thus, a “loading dose” and short-acting opioids may be indicated when initiating background pain management with regularly scheduled medications that have a long half-life (eg, MS Contin [Purdue Frederick, Norwalk, CT], Oxycontin [Purdue Pharma L.P., Stamford, CT], methadone, and so forth).

### Breakthrough Pain in the Healing Phase

Breakthrough pain during the healing phase is often associated with movement. Because of the critical need for mobilization of the burn-injured patient, effective management of breakthrough pain is critical to minimize the risk of complications (eg, respiratory infection, deconditioning, loss of function, and contractures). The time course of angiogenesis, neural regeneration, and reepithelialization during the healing phase of burn recovery warrants investigation to correlate it with changes in primary mechanical hyperalgesia, the major source of severe pain in burn-injured patients.

### Rehabilitation Phase

The rehabilitation phase is characterized by completion of wound closure, scar maturation, and aggressive physical and occupational therapy to stretch healing tissues, prevent contractures, and optimize functional outcomes. During the rehabilitation phase, complaints of on-going, spontaneous pain and/or paresthesias, dyesthesias, or allodynia in response to temperature changes, particularly cold, as well as neuropathic pain symptoms, may arise. Qualitative terms patients use to describe these sensations include phasic burning, tingling, prickling, and shooting sensations.

### Procedural Pain During the Rehabilitation Phase

The pain management needs of patients with burns usually decline markedly once healing (ie, wound closure) has occurred. In this case, opioids are usually not indicated for procedural pain during the rehabilitation
and adjuvants such as clonidine. Benzodiazepine withdrawal with tapering schedules may also be indicated. For moderate pain, oxycodone or a similar opioid preparation mixed with acetaminophen is indicated. Opioid medications are usually discontinued by the beginning of, or early in this phase. Because of the frequent need for large doses of opioid analgesics up until wound closure is accomplished, tapering of opioids may be indicated to avoid symptoms of withdrawal. Clonidine can augment opioid analgesia as well as diminish the hyperadrenergic symptoms of opioid abstinence and anxiety. Therefore, clonidine may be considered as an analgesic adjunct as well as an important adjuvant during opioid tapering. Benzodiazepine tapering may also be indicated. Although this important clinical issue is gaining attention, particularly in critically ill burn-injured children, research is needed to enhance the safe and effective management of opioid and benzodiazepine withdrawal with tapering schedules and adjuvants such as clonidine.

**Background Pain During the Rehabilitation Phase**

If wound closure has occurred, background pain may not be a problem during the rehabilitation phase of burn recovery. However, if open wounds remain, and background pain is an issue, the same principles suggested for the treatment of background pain during the healing phase apply.

**Breakthrough Pain During the Rehabilitation Phase**

Breakthrough pain associated with movement or stretching exercises may be significant, but this type of pain can often be anticipated, planned for, and treated as with a painful procedure.

**Pharmacokinetics and Pharmacodynamics After Burn Injury**

Burn injuries induce a profound inflammatory response that can affect changes in pharmacokinetics and pharmacodynamics, depending on the size of the injury (greater than 10% body surface area). Massive fluid resuscitation is necessary to maintain hemodynamic stability and to avoid “burn shock.” Thus, the primary route of administration during the acute phase is intravenous because of potential problems with enteral absorption related to decreased perfusion. Within days, a transition to a “flow” phase occurs that is characterized by increased resting energy expenditure and hypermetabolism that can last from several weeks to months to years after injury, depending on the size of the burn.

During the healing and rehabilitation phases, the metabolic rate of burn-injured patients increased by 50% when burn size was greater than 20% to 30% surface area and even greater in larger burns or if burn wound sepsis was present. Increased circulating catecholamines and adrenal steroid hormones are integral parts of this physiologic response thought to support recovery through compensatory cardiovascular, metabolic, and immunologic changes. Thus, concern for changes in pharmacokinetics and pharmacodynamics after burn injury can be a barrier to pain management.

Alterations in the pharmacokinetics and pharmacodynamics of a variety of nonopioid medications have been observed in burn-injured patients, ranging from serum protein shifts to target receptor desensitization or supersensitization. However, research suggests that elimination kinetics of morphine and lorazepam are not impaired after burn injury and that systemic clearance may actually be enhanced in larger burns (eg, up to 80% body surface area), beyond which clearance decreases toward control levels. Kealey and colleagues investigated the pharmacokinetics of morphine in patients with a mean body surface area burn of 21.5% in an attempt to ascertain a rational dosage schedule for patients with burns. Treatments included a morphine constant rate infusion followed by immediate release oral morphine solution and sustained release MS Contin. The half-life of morphine oral solution was 3 hours, whereas the half life of MS Contin was 14.7 hours. Time to peak levels with oral morphine solution was 30 minutes and time to peak levels with MS Contin was 1.4 hours. These data indicate that procedural, background, and breakthrough pain can be treated with the use of rapid-release oral morphine preparations for the recommended doses and that morphine sulphate sustained-release formulations are a good choice in the management of background pain in patients with burns given an 8- to 12-hour dosage schedule.

Choinière et al studied 5 patients with major first-, second-, or third-degree burn injuries that received a long-term intravenous morphine infusion. No differences were found in steady-state concentrations and systemic clearance of morphine, and its metabolites 3MG and 66G among patients with burns, other patient populations, and healthy volunteers receiving intravenously administered morphine over a period of 3 weeks. Among patients with burn injuries, the severity of burns and the duration of administration were not a cause of nonlinear kinetic variability of morphine or of morphine resistance. Although the morphine infusion rate was substantially variable, from 4 to 39.5 mg/hour, it was not directly related to its systemic clearance. Thus, until more data are available to the contrary, the monitoring of morphine should be focused on the clinical response and titrated to effect.

Intravenous local anesthetics are gaining interest but are rarely administered in most burn centers. Jonsson et al demonstrated that lignocaine infusion was safe and
strikingly reduced self-assessed pain scores in 7 patients during the first 3 days after second-degree burns, without need for supplementary opiate analgesia, but no pharmacokinetic data are available. The relatively short half-life of lidocaine, however, is advantageous because it is rapidly cleared following burn dressing changes and physiotherapy. In a study of healthy volunteers, small burns were induced before and after intravenous lidocaine administration. Local anesthetics administered in concentrations that did not block nerve conduction substantially reduced pain (primary and secondary thermal hyperalgesia). However, a significant preemptive effect could not be demonstrated. Although the antihyperalgesic effect of lidocaine probably is based on action at central (spinal) sites, peripheral sites may also be involved and research is needed to answer this question.78

As previously mentioned, topical application of local anesthetics has met with disappointing results. However, topical lidocaine may be safe and effective for control of pruritus, a major problem during the rehabilitation phase that can impede burn recovery. EMLA (a eutectic mixture of local anesthetics—prilocaine and lignocaine) was evaluated in a pilot study involving burned children. EMLA was used to ameliorate postburn pruritus after application onto newly formed, intact skin. Serial blood samples were collected in 5 children after 15.7 ± 2.54 g (mean ± SD) of EMLA was applied to a skin surface area of 93.0 ± 37.0 cm². Prilocaine and lidocaine concentrations were below toxic levels and o-toluidine was not detected. The mean number of pruritic episodes and antihistamine breakthrough doses were greater in the 2 prestudy control days compared with study day 3 (P = .01 and P = .03, respectively). Skin at the site of EMLA application remained anesthetized for 12 to 13 hours. These data suggest that EMLA may be a safe, novel treatment for postburn pruritus when applied to vulnerable newly healed skin.

Pruritus

Pruritus (eg, itch) commonly replaces pain as a source of significant anxiety and distress during the rehabilitation phase. Common pharmacologic interventions for pruritus include antihistamines (eg, H1 and H2 antagonists, including diphenhydramine, cyproheptadine, and hydroxyzine), and some burn centers have developed standardized protocols for the management of burn associated pruritus. Although few assessment scales exist, a pediatric “itch man scale” was created by Pat Blakeney and Janet Marvin, as described by Ratcliff et al. Not only is itching a source of anxiety and distress, but attempts to relieve the itch by scratching or rubbing jeopardizes newly healed skin, which is easily blistered and injured in response to mechanical stimulation.

Prevalence of pruritus after burn injury is high. Reports suggest that 60% to 87% of patients report either persistent (15%) or intermittent (44%) pruritus. Although oral pharmacologic agents are probably the most common method as described above, topical pharma-

macologic and nonpharmacologic agents, massage, and transcutaneous electrical nerve stimulation have also been studied to manage pruritus. However, these studies lack the evidence to make treatment recommendations.

Chronic Burn Injury Pain

Chronic pain has been identified as a significant problem many years after burn recovery. In a study that surveyed members of the Phoenix Society for Burn Survivors, 52% of respondents reported on-going burn-related pain an average of 12 years after injury (n = 348, 24% response rate). Other studies indicate that on-going pain, years after burn injury, is a significant problem. Complaints of chronic pain may first arise during the rehabilitation phase of burn recovery. It may initially present as hypersensitive or hyposensitive areas that develop in healed sites. Although hypersensitivity in newly healed skin is common, it often depends on the location, with the scalp, axilla, perineum, and the hands and feet being particularly sensitive for up to 1 year after injury at these sites. Loss of sensibility is more common after deep burns and grafted injuries. In a study of 236 patients who responded to a survey (67% response rate) at least 1 year after burn trauma, more than one third of participants complained of pain. A total of 71% of patients complained of noxious paresthetic sensations, and only 28.4% of this sample reported no sensory problems. In an effort to define the extent of cutaneous sensory dysfunction after burn injury, subjective reports of abnormal sensations were compared between patients with healed burns and normal control subjects. Physiological measures of tactile, thermal (nonnoxious), and pain thresholds were assessed in the upper extremities of 121 patients with healed burns, more than 18 months after injury, and compared with pair-matched control subjects. Whereas more patients with deep dermal burns that had required skin grafting reported significant sensory loss than patients with superficial dermal burns that had healed spontaneously, some patients reported increased sensitivity in their healed burns. Of note, the majority of patients who had decreased thresholds also reported painful or paresthetic sensations at the site. Depth of burn was the only factor associated with the severity of sensory deficit, explaining more than one third of the observed variability. Patient age, sex, and medical variables, such as size of burn or time elapsed since the injury, did not explain a significant proportion of the variation in the sensitivity thresholds in this study. Of note, sensory loss was observed in burn sites as well as uninjured areas, which suggested to these authors that changes may have occurred in the central nervous system. However, in an animal model of full-thickness burn injury, receptive fields were found to usually extend into both adjacent and noncontiguous skin, which is consistent, as these authors point out, with the anatomy of terminal fields of cutaneous nociceptors that can be...
quite extensive, stretching over several millimeters, or centimeters.

Although few studies have evaluated their effect on chronic pain after burn injury, centrally acting agents used to treat neuropathic pain, including antidepressants (eg, amitriptyline), anticonvulsants (eg, gabapentin), and clonidine may prove useful in this patient population. In addition, benzodiazepines are useful adjuvants due to their anticonvulsant properties; and NMDA antagonists, such as ketamine and dextro-methorphan, may be useful as NMDA receptors play a role in central sensitization after experimental burn injury.

In deep partial-thickness burns, thermal injury causes primary afferent axons to swell, degranulate, and demyelinate. Macrophages invade the degenerating nerve stump, removing myelin and axonal debris but leaving the basal lamina intact through Wallerian degeneration. In addition, excision of eschar, sharp debridement of devitalized tissue, and further ischemia in the zone of tissue surrounding the burn wound induce peripheral nerve damage. Indeed, the term “phantom skin” was introduced by Atchison et al in response to their observation that the pain of burns is often resistant to opioids, similar to neuropathic pain.

The preferential loss of large fibers in burn scar and graft tissue may contribute to the incidence of neuropathic pain, consistent with the gate control theory. The rate of degeneration may also play a role in chronic burn pain similar to isoniazid neuropathy, as patients may initially complain of numbness and tingling paresthesias that are later accompanied by pain. In thermal burn sites, neurons were shown to be completely absent in human tissue 2 days after injury and remained undetectable for 10 days. As damaged neurons regenerate, abnormal ectopic excitability at or near the site of nerve injury may develop due to unusual distributions of sodium (Na⁺) channels and abnormal responses to endogenous pain producing substances, including cytokines such as tumor necrosis factor-α. Persistent abnormal excitability of sensory nerve endings in a traumatic neurona, the mass of nonneoplastic Schwann cells, and neurites that may develop at the proximal end of a severed or injured nerve is considered a mechanism for amputation-induced pain, which may also play a role in the development of burn-induced chronic pain. Local nerve injury tends to spread to distant parts of the peripheral and central nervous system. For example, damage to neurons in the periphery has been found to contribute to changes in the spinal cord that may in turn contribute to neuropathic pain. It follows that damage to sensory neurons may be a mechanism for burn injury–induced neuropathic pain, but this question has not been studied.

Another cause of chronic pain after deep burns involves the frequent practice of tangential and/or fascial excision of eschar associated with these injuries. This practice may cause intact peripheral afferent nociceptors to become injured. It also seems likely that regeneration of neurons from wound margins may contribute to burn pain.

Few studies have examined neural regeneration in human autograft and healing skin after burn injury. Of these, only 1 obtained comparison samples from the same patients, making it possible to determine changes with control skin in the same patient over time. Sensory measures of pinprick, warming, touch, and vibration were all significantly decreased (all P < .001) in burn-grafted skin, with thermal threshold showing the greatest degree of functional recovery. These findings correlated with histologic analysis of skin biopsy specimens from the same site that showed a significant reduction in the axons that innervated the dermis and the epidermis in burn graft relative to control skin (54% decrease, P < .0001). Of note, the number of neurons that expressed substance P was significantly elevated in the autografted site and appeared to correlate with patient reports of pain and pruritus (P < .05). These authors concluded that sensory regeneration may be fiber size–dependent in burn-graft skin, with substance P–containing fibers predominating but total fiber count decreasing. These data support the hypothesis that unmyelinated neurons have a greater ability to traverse scar tissue and reinnervate grafted skin after full-thickness burn injury. However, no correlation was reported between these findings and pain severity scores.

Basic Science Models of Burn Injury Pain

Few basic science models have been available to study burn injury pain. Although human models have been introduced, it is difficult to separate the mechanisms of burn injury pain in humans. More recently, however, several animal models have been introduced that make it possible to begin to tease apart the complex mechanisms that contribute to the variability and intensity of burn injury pain over time.

In experimental animal models, second-messenger proteins, including protein kinase C-epsilon (PKCe), and neurotrophins such as nerve growth factor (NGF) and neurotrophins such as nerve growth factor (NGF) have been identified as significant mediators of acute burn-induced hyperalgesia. These mediators may also play a role in chronic burn pain. PKCe has been found to mediate priming, a predilection toward the development of chronic hyperalgesia in a previously healed site of inflammation, and NGF induces hyperalgesia in noncontiguous, uninjured skin after burn injury in rats. NGF is also found in newly formed epithelial cells at the edge of wounds. The study of peripheral mechanisms in chronic pain after burn injury is a high priority for future research.

Why is Burn Injury Pain Still a Major Problem After 20 Years?

Although the problem of undertreated burn injury pain was well described more than 20 years ago and despite a call to make pain the highest research
priority in burn care due to its detrimental effects on patients as well as those who care for them more than 15 years ago, burn injury pain remains a continuing challenge. Recent publications report unacceptably high pain ratings (mean, 7/10) for procedural pain and chronic pain 4 months after injury. Clinical observations confirm that these reports are not unusual. This is discouraging when one considers the wide availability of pain management guidelines and the promotion of guideline-based treatment approaches. Unlike surgical pain that subsides gradually, burn injury pain is highly variable and may increase over time, much to the patient’s distress, before healing is accomplished. This makes approaching burn injury pain with the World Health Organization’s analgesic ladder or titrating to effect often impractical. In fact, the ladder could be applied in reverse to this patient population, with the use of the most potent analgesics, opioids, first. However, like other health care providers, those who care for burn patients must balance the dichotomy of knowing that opioids can be used for analgesia as well as for abuse. Moreover, it is valid to question the safety of the administration of opioids in patients with major burns. Because of their requirement for massive fluid resuscitation during the first few days after admission and the potential for contributing to hemodynamic instability, it has been recommended that patients such as these not be administered more than 10 mg of intravenous morphine sulfate in a 24-hour period. This is a small amount compared with what is administered to most burn-injured patients, although, as pointed out by Choinière, the opioid doses reported in some studies to patients with much smaller injuries are barely within the range required to control much less intense types of pain. In addition, burns are profoundly immunosuppressive, and there is a large body of literature that suggests opioids may contribute to immunosuppression. High risk for mortality and morbidity frequently places their safety above their need for pain management.

Nonetheless, perhaps it is time to stop insisting that burn pain is a very difficult type of pain to treat and question if we are doing the very best to treat it. Are burn centers using the principles of multimodal analgesia (eg, different classes of medications in combination with nonpharmacologic methods) in a systematic manner? As previously mentioned, nonsteroidal anti-inflammatory agents are usually contraindicated in this patient population, but other medications are rarely used even though they appear to be very useful for pain management in the burn-injured patient. For example, clonidine, ketamine, lidocaine, and methadone appear to be underused in this patient population. However, their use may decrease the need for rapidly acting, potent opioids usually required for painful procedures. Moreover, the use of mixed μ-receptor antagonists and/or agonist-antagonists may prevent or ameliorate tolerance that is so commonly observed in patients with major burns.

We also need to ask, are members of the multidisciplinary burn team aware of the most recent data on pain and analgesia, and is this information being implemented by those who care for burn-injured patients? Those who specialize in the care of these patients may become accustomed to the expectation that pain will not be controlled, particularly during procedures. One may rationalize that it will only hurt for a brief period of time, but research suggests that peak procedural pain and global recollection of procedural pain are correlated and that global recollection of procedural pain (ie, 4 hours immediately after surgery) influences patient satisfaction.

Fentanyl has been demonstrated to be the most effective analgesic for burn procedural pain, but do patients receive a dose of this potent and short-acting opioid in time to meet their need for peak procedural pain relief or are we prevented from helping some patients in this manner due to the fear of overdosing others in the same manner? Research is needed to expand our vision for assisting this vulnerable patient population. The judicious use of diluted naloxone and flumazenil reverses the effects of opioids and benzodiazepines, but they are rarely used to avoid oversedation and other side effects that frequently limit the use of opioids and benzodiazepines. As suggested by Silbert et al, although new therapeutic approaches are desperately needed, we do not need to wait on basic science. Alternatives are readily available at the bedside today. Are nonpharmacologic as well as pharmacologic interventions systematically implemented? Are we using new materials, such as dissolvable staples to minimize procedural pain, unless contra-indicated? Is the pain plan visible? That is to say, is the pain management plan systematically evaluated, to keep pace with the patients’ rapidly changing needs and made visible for the burn management team?

Importantly, we also need more research on burn injury pain. The American Burn Association Patient Registry Participant Group and The National Institute on Disability and Rehabilitation Research Burn Model System Database developers may be well positioned to make recommendations as to how information could be tracked similar to their important work tracking outcomes in the treatment of burn trauma in the United States. Until we have the science, we will continue to lack a basis for rationale treatment recommendations for acute and chronic burn injury pain. In particular, research is needed to identify the underlying mechanisms for burn injury pain over time. Only with this knowledge will burn care providers be able to target specific mechanisms that contribute to the variable intensity that makes this type of pain such a difficult management problem.

Conclusion

Burn-injured patients of all ages have procedural, background, and breakthrough pain during the acute, healing, and rehabilitative phases over the long course of burn recovery. The establishment of multidisciplinary burn team and institutionally supported system changes...
that will promote the recognition and implementation of changes necessary to accomplish safe and effective burn pain management are critically needed. Moreover, research that focuses on the continuing challenge of burn injury pain is critically important. Only with these valuable data can the efficacy of acute and chronic burn injury pain be improved and the underlying mechanisms finally understood and rationally treated.

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