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Pathophysiology and management of burn injury-induced pain

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Abstract

This review examines the pathophysiology and therapeutic management of burn injury-induced pain (BIP). Burn injury, occurring globally in about 11 million people, often induces the most intense pain, but its management remains suboptimal. The pain often persists even after complete wound healing and hospital discharge causing both long-term disability and neurological dysfunction. The fact that BIP persists well beyond the initial hospitalization is not well recognized and should be underscored as the pain involves even non-burned areas. The pathophysiology of the latter problem is poorly understood and needs further study. Opioids, the mainstay for moderate to severe pain relief after major burn injury, with time, have poor analgesic and serious side effects. Accurate assessment pain of BIP and its biology at different stages of treatment helps to provide effective treatments of the different etiological factors that cause BIP and their sequelae. Based on clinical and pre-clinical studies, we discuss the current knowledge on the underlying cellular and molecular mechanisms in the initiation and persistence of BIP during the acute phase and later phases of injury. Opioid receptor-mediated signaling changes *per se* and immune microglia responses in concert exaggerate nociceptive behavior. Both burn injury and opioids upregulate spinal NMDA receptor expression and microglia changes, which further exaggerate pain. BIP has inflammatory and neuropathic components. Pharmacological and non-pharmacological approaches currently available for management of BIP is discussed. Areas that need further study include the role of other central and peripheral factors in the exaggeration of pain well beyond wound healing. Novel non-opioid methods to rectify BIP is important to develop in view of the potential for opioid use disorder. The role of microbiome in chronic pain syndromes is an unexplored territory and its relevance to BIP needs further examination. Pruritus or itch, though very common and important in the pharmacotherapy of burns, the discussion of this topic is brief. Extensive review of this topic is beyond the scope of this review in view of the vast body of knowledge and varying and multiple treatment options.

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Declaration of competing interest

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Keywords

Burn injury; Pain; Inflammation; Neuropathic; Opioid

1. Introduction

Globally about 11 million people suffer some form of burn injury (BI) per year [1]. Nearly half a million burn injuries occur throughout the United States every year [2]. BI can produce the most physically debilitating and traumatic injuries due to their systemic effects on the body that can lead to significant morbidity and mortality [3]. One of the most debilitating aspects one observes during the care of BI subjects is the pain that these patients experience from the onset of injury, during the recovery and the rehabilitation period and in some instances even beyond full wound healing and hospital discharge [4]. The burn injury-induced pain (BIP) continues to be a major challenge for burn care providers because of the very dynamic and changing nature of the pathophysiological responses during the acute and recovery phases of injury. BIP consists of a combination of background pain, procedural pain, breakthrough pain, postoperative pain, and chronic pain that can extend beyond the recovery and wound healing period [4–6]. BIP management is particularly challenging because the interventions used to enhance healing of burned can actually be the greatest source of exaggeration of pain. These include daily dressing changes, surgical debridement, physical therapy, new insults from donor sites and excision of burn injury sites [7].

Although these aspects are well recognized and expertly described, BIP continues to be poorly managed because clinical management does not always correlate with the personalized experience of patients. It is of utmost importance to aggressively control pain because uncontrolled pain can lead to a plethora of long-lasting effects and side effects: loss of confidence between patient and team members, poor wound healing, aggravated hypermetabolism and protein catabolism, immunological dysfunction, increased morbidity and mortality, development of psychiatric disorders including delirium and maladaptive behaviors initially and long-term depression, post-traumatic stress disorder (PTSD), sleep disturbances [8] and even opioid use disorder [9,10]. The difficulty of treating BIP with pharmacologic agents is further complicated by the various metabolic derangements that are associated with burn injuries. The multifaceted nature of BIP encompasses anatomic, metabolic, and psychological factors and poses a significant challenge for clinicians. Previously, a Boston group (included JAJM) has reviewed “opioid tolerance in critical illness” [11]. This previous review did not address specific issues related to burn injury [11]. The current review seeks to explore the pathophysiologic mechanisms behind BIP and its clinical management. We highlight the role of neuro-immune interaction, especially that of spinal microglia activation and microglia as a potential therapeutic target for BIP treatment based on more recent preclinical studies [12,13].

2. Pathophysiology, cellular, and molecular mechanisms of burn pain

BIP has been shown to have inflammatory and neuropathic components that act in concert to cause the aggravated pain behaviors in humans, whose perception can be further modulated by ways that are yet ill-understood and include genetic, environmental, mood, anxiety context, and pharmacologic factors.

2.1. Neuropathic pain as a component of burn pain

Major BIP has neuropathic and inflammatory pain components. Partial nerve injury and injection of Freud's adjuvant have been used to study the neuropathic and inflammatory components pain, respectively [14]. When skin is damaged by burn, heat activates pain-sensing neurons (nociceptors) in the affected area, resulting in nociceptive pain. Damaged tissue triggers inflammatory responses, immune cells (e.g. skin resident immune cells, neutrophils, macrophages,) release inflammatory mediators [15], such as histamine, serotonin, bradykinin, leukotrienes, and prostaglandins, etc. that sensitize nociceptors intensifying the pain sensation. These immediate pain sensations are elicited by activity in the unmyelinated C- and thinly myelinated A-delta (Aδ) fibers of nociceptors [16] (Fig. 1). In burn treatment, dressing change causes significant accentuation of the nociceptive pain. Other treatment procedures, such as surgical debridement, grafting, and physical therapy, also directly stimulate nociceptor causing exaggerated procedural pain. This feature is exemplified by the recent use of a prescription medicine, Nexobrid® (anacaulase-bcdb), used to remove dead skin tissue, or eschar, from thermal burns in adults and children, which causes severe exaggeration of the basal pain during its application [17].

Neuropathic pain has been detailed as a source of pain in burn injury due to abnormalities in regenerated nerve endings and deficiencies in reinnervation of scars [8]. Due to these nerve changes, chronic, persistent component of burn pain has traditionally been regarded as neuropathic pain. However, acute neuropathic pain has also emerged as a significant component of BIP [18,19] due to burn-induced damages to nerve endings, and often goes under-recognized and under-treated [20,21]. Peripheral sensory nerves and descending tracts from cortical areas can also modulate the severity of the pain. Markers of burn-induced neuropathic components to BIP include increased expression of N-methyl-D-aspartate (NMDA) receptor [12]. Increased expression of tissue IL-6, which signals downstream through STAT-3 (signal transducer and activator of transcription 3), can also be considered a marker for neuropathic pain. In a young rat model, burn injury caused changes in signaling proteins within the spinal cord dorsal horn ipsilateral to burn injury, including upregulation of the NR1 subunit of the NMDA receptor, serine-threonine protein kinase Akt1, Akt2 (also known as protein kinase B), and protein kinase C γ (PKCγ) and downregulation of the neuronal nitric oxide synthase (NOS), inducible NOS, and glycogen synthase kinase-3β [22]. Nerve injury-associated neuropathic pain also induces expression of spinal nuclear glutamate receptors, which can aggravate pain [23]. The concomitant administration of midazolam and/or morphine exaggerates neuropathic pain behaviors as reflected by increased spinal expression of NMDA receptor [24]. Due to changes in pain signal transducers in the spinal cord, the dorsal horn neurons become hyperexcitable and display increased evoked activity initially on the ipsilateral side to the burn injury

and eventually involve the contralateral side too. The hyperactivity of glutamate receptor provides the rationale for the use of ketamine to treat neuropathic pain.

Regardless of the above enumerated factors, the ultimate conscious perception of pain, however, has been found to involve higher cortical areas, such as the thalamus [25]. Using active transcranial direct current stimulation, a study showed that patients with chronic neuropathic pain have defective intracortical inhibition as a central neural mechanism [26]. Due to these complex peripheral and central factors, several pharmacologic regimens have been explored for the management of acute and chronic neuropathic components of pain in burn patients.

2.2. Inflammatory pain as a component of burn pain

Microglia, the resident macrophages of the central nervous system (CNS) together with the peripheral macrophages comprise part of the innate immune system [27]. During damage or environmental changes, they respond by transforming and/or migrating to the area of injury. Burn injury leads to systemic and neuro-inflammatory responses. Burn injury induces microglial proliferation and activation [13,28], together with pain (Fig. 1). In unilateral focal burn injury on the hind paw, we and others [28–30] have observed increased expression of the markers for microglia (Iba-1, ionized calcium-binding adaptor molecule 1) and astrocyte (GFAP, glial fibrillary acidic protein); activation of microglia p-p38 mitogen-activated protein kinase (MAPK) signaling and astrocytic JNK/CXCL1 pathway; and inflammatory cytokines TNFα (tumor necrosis factor-α), and IL-1β (interleukin-1β) in lumbar spinal cord segments. In a mouse model of burn injury affecting 35 % body surface area [31], neuroinflammation was evidenced by upregulation of neuro-inflammatory markers, the inflammatory cytokines and inflammatory chemokines (CXCL2) released by microglia [12,30]. After burn injury, macrophages rapidly accumulate at the site of burn and release proinflammatory cytokines and play an important role as a mediator of BIP [32]. In the skin of burned rat, the level of IL-6 is increased, possibly released by macrophages. Subcutaneous injection of IL-6 mimicked the pain of partial-thickness skin burn injury of a rat on the ipsilateral side to the burn [33], but not contralateral side which probably explains the prolonged ipsilateral hyperalgesia seen in burn patients.

2.3. Neuroimmune interaction in burn pain: cholinergic anti-pathways and sympathetic nervous systeminflammatory pathways and sympathetic nervous system

The autonomic nervous system can play a role in the regulation of innate responses and inflammation. The injury- and/or infection-related release of damage-associated molecular patterns (DAMPs), pathogen associated molecular patterns (PAMPs) and the inflammatory cytokines are detected by afferent sensory neurons generating a central nervous system-initiated immunomodulatory response mediated through efferent autonomic nervous system. Thus, the brain monitors and has the potential to integrate innate immune communication via the autonomic nervous system.

In the recent past, increasing attention has been paid to the immune modulation by the so-called cholinergic anti-inflammatory pathway (CAP) predominantly controlled by the vagus afferent and efferent to counteract the pro-inflammatory immune responses [34].

Studies over the last 20 years have provided substantial understanding of efferent pathway which involves the sympathetic ganglion and spleen immune cells [35]. The alpha 7 nicotinic acetylcholine receptor (α7AChR) is the primary receptor expressed in the immune cells that affects the anti-inflammatory properties of this pathway and is upregulated on microglial cells during burn injury. Acetylcholine is the endogenous agonist of the α7AChR, which when stimulated exhibits anti-inflammatory properties evidenced as lowering of pro-inflammatory molecules (decreased expression of cytokines, chemokines and adhesion molecules) by altering the differentiation and activation of immune cells. An exogenous agonist of α7AChR, GTS-21, elicited antinociceptive effects in a rat burn model and showed promise as an adjunctive agent to attenuate BIP [12].

Variable information is available on the role of the sympathetic nervous system (SNS) in pain. The SNS can interact at many levels and can suppress pain or exaggerate pain [36]. The anxiety and the pain and the metabolic responses to injury lead increased sympathetic activity. The “fight or flight” response of injury can amplify pain signals by increasing sensitivity to stimuli and contributing to the phenomenon known as “sympathetically maintained pain” where pain is directly influenced by heightened sympathetic activity. This theory is exemplified by the observation that sympathetic block of some nerve fibers improves pain [37]. Recent studies, however, have identified that the carotid body (CB), a blood oxygen sensor, acts as a sensor of peripheral inflammation and plays a critical role neuroimmune interaction [38]. Experimental evidence indicates that the CB detects immunological disturbances reflected by increased levels of inflammatory cytokines (e. g. TNFα) in the circulation and activate brain sympathetic output to suppress inflammation by activating splanchnic sympathetic anti-inflammatory mechanism [39]. Thus, the SNS can interact at many levels and can suppress pain or exaggerate pain; unraveling the detailed molecular mechanisms of how this interaction of SNS and pain is established in health and disease will help us to treat burn pain more successfully in the future [36].

3. Opioid tolerance and opioids in the aggravation of burn pain

Opioids have been considered the backbone for the multi-modal pain management regimen most frequently used to manage BIP. At least initially, opioids are the most effective drugs for the treatment of moderate to severe pain. Compared to many other analgesic drugs, opioids are readily available and fairly inexpensive [6]. Hence, they are widely utilized throughout all phases of BIP. However, it is not un-common for patients to begin manifesting increased opioid requirements that exceed the standard guidelines due to the cycle of hyperalgesia and tolerance that develops [11,40].

Clinical observations have also confirmed that hyperalgesia in populations with critical illnesses, such as burn injury, can be more pro-found than in the general population [41]. These aspects make burn pain management particularly difficult. One mechanism of hyperalgesia stems from the opioid-induced neuroinflammation that occurs when opioids activate toll-like receptor 4 (TLR4) [42] in the glia and other immune cells that permeate the blood–brain barrier, even in the absence of blood–brain barrier breakdown [11,43]. The cytokine release from immune cells leads to lowered pain thresholds and exaggerated nociception (hyperalgesia). The exaggerated and prolonged pain in burn

injury requires repeated high dose of opioids for pain management, which often leads to the development of opioid tolerance. Tolerance (decreased responses to the same dose) occurs due to desensitization of opioid receptor and suppression of receptor-mediated antinociceptive pathways [11]. Opioid tolerance can be caused by several mechanisms. One of the mechanisms is the downregulation of opioid receptor MOR (μ receptor) and its phosphorylation. In rats with burn injury-associated tolerance to morphine, the μ receptor level was decreased in the spinal cord [44]. The continued administration of opioids results in development of pronociceptive signaling pathways. These include attenuation of the decreased intracellular calcium uptake by opioids, increase in hyperpolarization and upregulation of adenylate cyclase activity [11]. It is the latter that causes tachycardia and hypertension during abrupt opioid withdrawal after prolonged administration.

There are multiple factors (inflammation, infection, stress, and opioid use) that can lead to glial activation and exaggerate pain bhaviors, tolerance, and hyperalgesia, creating a cycle of dose escalation and worsening pain [11]. Many strategies have been explored to combat this vicious cycle of opioid-induced hyperalgesia and tolerance. For instance, reducing the dose and duration of treatment by interrupting infusions of sedatives or analgesics daily or modulating infusions on the basis of analgesic assessment and sedation scores, using multimodal techniques, and rotating analgesic agents have all been documented [11]. Intravenous patient-controlled analgesia has shown clinical success as a means of providing flexible analgesia to patients [45]. Due to the complex nature of pain in burn patients, an understanding of the mechanisms and options for clinical management will result in better patient care.

4. Clinical management: opioid and non-opioid pharmacologic approaches

The BIP can be due to a combination of background pain, procedural pain, breakthrough pain, surgery-induced postoperative pain, and chronic pain that extends beyond the rehabilitation period [6]. Due to the multifaceted nature of BIP that stems from interactions between neuronal and non-neuronal (e.g., glia) components, it is of utmost importance to prioritize a multimodal regimen that utilizes opioid and non-opioid pharmacologic strategies. Burn pain has hyperalgesic (increased response to painful stimuli) and allodynic components (painful responses to non-painful stimuli) [40]. In all phases of BIP, anxiety can exacerbate the pain if it is poorly controlled.

4.1. Background pain

Background pain is a result of thermal injury to the tissue itself and the resultant inflammatory and neuropathic responses to the injury. This pain is proportional to the size of injury [46]. It usually occurs while at rest, is of low to moderate intensity, and has a long duration. This type of pain must be addressed before procedural and postoperative pain can be controlled. Background pain is usually managed with opioids, either via oral or continuous IV infusion or patient/nurse-controlled analgesia (PCA), but patients frequently develop tolerance so the dose requirements should be assessed frequently. In order to prevent opioid-induced hyperalgesia and increasing doses, other pharmacologic agents can

be used as adjuvants. For instance, acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), ketamine, and alpha-2 agonists can be co-administered. Acetaminophen and oral NSAIDs are the agents of choice for minor burns, but are unsuitable for major burns because they exhibit a ceiling effect in their dose–response relationship [21]. NSAIDs are also associated with renal tubular dysfunction and have adverse effects on gastric mucosa by causing gastric hemorrhage. Alpha-2 agonists, such as clonidine and dexmedetomidine, are particularly helpful to prevent withdrawal symptoms from narcotic and benzodiazepines [46]. However, the alpha-2 agonists can cause hypotension in the presence of hypovolemia and in higher doses, so should be avoided in hemodynamically unstable patients [47]. Due to the pro-longed nature of background pain, it can lead to depression and anxiety which should be managed with anti-depressants, antipsychotics and/or benzodiazepines [46].

4.2. Procedural pain

Procedural pain is the greatest source of pain for burn victims and occurs during procedures such as dressing changes, surgical debridement, or physical therapy [7]. Many regimens have been explored, but providing adequate pain control during this phase continues to be a challenge. Most of these regimens include boluses of opioids, sedatives, and/or ketamine [46]. Due to the development of tolerance to narcotics in burn patients, ketamine has been selected in many situations [46]. However, boluses of ketamine can cause hypotension despite the ketamine-induced catecholamine release. The increased levels of catecholamines can desensitize and downregulate beta-adrenoreceptors, which causes a direct myocardial depressant effect [48]. In addition, there is an upregulation of NMDA receptors in the dorsal horn of the spinal cord, which may lead to increased ketamine requirements [1]. To combat these side effects, a study discovered that the combination of ketamine, tramadol, and dexmedetomidine is an excellent treatment option for the prevention of the procedural pain [49]. Another commonly used combination is the use of NSAIDs and anti-psychotics with opioids [40]. Procedural pain is also associated with anxiety, which can further exacerbate pain. Due to this, anxiolytics and low-dose benzodiazepines can be administered [50]. However, the use of benzo-diazepines should be minimized or used with caution due to the association with short-term and long-term delirium. Additionally, the long-term administration of midazolam, a benzodiazepine, has been shown to exaggerate tolerance to opiates [24]. Antipsychotics, such as quetiapine and haloperidol, can also be utilized if there is increased agitation associated with the anxiety. Tolerance can develop to most sedative and analgesic drugs used during burn care because of the prolonged recovery and therefore extended use of these compounds should be minimized and drug rotation practiced [6,11].

4.3. Breakthrough pain

Breakthrough pain is described as an unexpected exacerbation of pain when the background analgesic effect is exceeded [6]. This can occur at any time—during rest, procedures (both dressing changes and operating room events), or with stress. The management of breakthrough pain is comparable to that of background pain. Similar agents are used, with opioids being the mainstay of treatment. Non-opioid agents, such as oral NSAIDs and acetaminophen, can be utilized if tolerance develops. The main difference is the dosing–background pain uses pre-emptive, regular dosing while breakthrough pain is managed with

supplemental, “as needed” dosing [51]. Multi-modal approaches with other drugs could be added with time.

4.4. Postoperative pain

Postoperative pain is a temporary, but expected pain that occurs after donor skin harvesting, burn excision, grafting, or other interventions due to the creation of new wounds [6]. Inadequate control of pain after surgery or procedures has the potential to negatively impact wound healing and can have long-term psychologic effects on the patient. Over time, it is very common for patients to develop a tolerance to analgesics and sedatives. Due to this, increased doses may be required, especially in the postoperative period [40]. Other non-opioid agents, such as alpha-2 agonists and NMDA antagonists, can provide benefits. Gabapentin has also shown clinical potential in the treatment of post-operative pain by reducing primary mechanical allodynia in acute inflammation after burn injury [52]. No controlled study exists as to utility and efficacy of gabapentin and related drugs in the treatment of BIP.

Regional anesthesia techniques have been found to be particularly useful at this stage and are increasingly used in BIP [17,53]. They can provide intraoperative anesthesia, postoperative analgesia, and even expedite the rehabilitation period. Regional anesthesia can be utilized for burn wound pain and donor site pain. Usually, patients have more intense pain from the split-thickness skin donor site than the grafted burn wound [40]. Regional anesthesia techniques can include tumescent local anesthesia injected into a donor site, subcutaneous catheter infusions, peripheral nerve, or central neuraxial blocks.

A study showed that continuous local anesthetic infusion with the use of a subcutaneous catheter placed immediately after split-thickness skin graft provided adequate pain control with no cases of donor site infection [54]. Central neuraxial blocks, such as spinals and epidurals, are effective but need to be carefully utilized in only certain populations due to the risk of infection with intravascular catheters if placed in or near burned tissue [55]. Truncal blocks (paravertebral and transversus abdominis) have been performed for donor site harvesting and can be placed as catheters to provide prolonged postoperative analgesia [40]. The lateral femoral cutaneous block is of significance because it an exclusive sensory nerve that innerves the lateral thigh, which is commonly a site for split-thickness skin grafts. If the anterior and middle thigh require coverage, a fascia iliaca block can be administered [55].

4.5. Chronic pain

Chronic pain persists for longer than six months or remains after all burn wounds and donor sites have healed [6]. Neuropathic pain is the most common form. Opioids, particularly morphine, were the choice previously. Now with the ongoing opioid epidemic and legislation related opioid prescriptions for prolonged periods, the use of opioids for a prolonged period has diminished and not the prioritized option [56]. Thus, the management of chronic pain poses a challenge because of the injury and opioid-induced hyperalgesia. Because of the previously induced tolerance and hyperalgesia, methadone has been used as a popular second-line opioid agent. It is a synthetic opioid drug with a prolonged

half-life compared to other opioids. It has a variable cytochrome P450-dependent metabolic half-life and cardiac toxicity [57]. Thus, use of methadone requires careful titration and close observation by experienced caregivers. In addition to binding the opioid receptor, methadone exerts a weaker analgesic effect via spinal NMDA receptor antagonization and on central serotonin and norepinephrine uptake [58]. A case study even reported significant alleviation of pain with methadone within a few days of after other agents (long- and short-acting opioids, amitriptyline, clonazepam, and gabapentin) failed to relieve pain [59]. Antidepressants continue to be utilized to manage depression, but have also shown clinical significance in enhancing opiate-induced analgesia, especially in patients with chronic neuropathic pain [40].

Chronic pain is often accompanied by post-burn pruritus during wound healing, especially on burn scar tissue [60]. Post-burn pruritus has both pruritogenic and neuropathic components. The mechanisms underlying post-burn pruritus have not been fully elucidated as post-burn pruritus is under-studied. Many treatment protocols are available, but these protocols reflect empirical approaches without a consensus on the best single treatment. Clinically, post-burn pruritus tends to be intractable to conventional treatments such as antihistamines or topical and systemic corticosteroid for pruritogenic pruritus [61]. Post-burn pruritus may or may not respond to neuroleptic agents such as gabapentin and pregabalin. Despite limited information gabapentin is widely used as an adjuvant to standard analgesia for acute and chronic neuropathic burn pain. Gabapentin has shown efficacy in ameliorating burn-induced hyperalgesia and allodynia, although this was not a controlled study [6]. Antagonists of histamine receptors H1 and H2 have been commonly used to control burn wound pruritis. The combination of cetirizine and cimetidine has demonstrated dramatic improvement in post-burn pruritis [62]. High intensity lasers and CO2 lasers are also being tried to mitigate pruritus of burns [63]. Based on the multiple approaches that have been recommended in a recent review, akin to treatment of BIP, adequate and patient satisfaction management of BIP is unresolved [63].

4.6. Burn pain assessment

Reliable evaluation of pain in all stages of burn care is critical for burn pain management. Pain should be assessed several times a day during various phases of care. Considering the depth and location of burn and the patient’s communication ability, various tools and techniques can be employed. For patients who can self-report their pain level, validated pain scales such as the Visual Analog Scale (VAS) or Numeric Rating Scale (NRS) can be used [5]. For patients unable to self-report, observational pain scales like the Critical Care Pain Observation Tool (CPOT) can be combined with physiological indicators like heart rate and blood pressure. During hospitalization, evaluation of anxiety should be included in the pain assessment. The Burn Specific Pain Anxiety Scale (BSPAS) has been proven as a validated tool.

5. Pharmokinetic component to the increased dose requirement

There are two distinct phases that occur in burn injuries: a burn shock phase followed by a hypermetabolic phase [64]. These phases significantly alter the pharmacokinetics and pharmacodynamics of drugs used to treat BIP.

From a pharmacokinetic standpoint, there are alterations in bioavailability, protein binding, and clearance [65]. Bioavailability of large, hydrophilic molecules is increased due to enhanced intestinal permeability. There is significant plasma protein loss through the skin and dilution of these proteins due to fluid resuscitation [40]. These changes can decrease the concentration of albumin, which is an important drug-binding protein. There is an increase in volume of distribution of several drugs, including propofol, fentanyl, and muscle relaxants [64]. This can be due to altered protein binding or an enlarged extracellular fluid volume [65]. In addition, hepatic enzyme activity is altered because phase I reactions —oxidation, reduction, hydroxylation, and demethylation—are impaired (e.g., diazepam). Phase II reactions—conjugation, glucuronidation, acetylation and sulfation—of drugs such as lorazepam and morphine are relatively unaffected [66]. From a pharmacodynamic standpoint, the changes at target organs can affect drug-receptor interactions causing variable and unpredictable changes in response to drugs [40]. Due to these metabolic factors, adjustments in the usual dosage of drugs may become necessary in burn patients.

The initial burn shock phase occurs within 48 h of burn injury and is characterized by decreased cardiac output, increased systemic vascular resistance, decreased hepatic and renal blood flow with decreased glomerular filtration rate, despite adequate fluid resuscitation [40]. The hepatic clearance of blood flow-dependent drugs depends heavily on hepatic blood flow and is relatively insensitive to changes in protein binding. These changes result in decreased renal and hepatic clearance of drugs and a slower rate of drug distribution. Hypoalbuminemia is observed due to several factors, namely increased vascular permeability that produces exudation with protein loss through the burn [67]. Since albumin binds to acidic and neutral drugs, their free fraction can significantly increase [68].

The second phase, which occurs 48 h after burn injury, is termed the hypermetabolic phase. This phase that usually follows resuscitation is characterized by a hyperdynamic state with increased cardiac output, decreased systemic vascular resistance, and increased renal and hepatic blood flow which leads to increased clearance of drugs that have flow-dependent elimination [40]. There is increased clearance, central compartment volume, and total volume of distribution of fentanyl in this phase, which results in lower plasma concentrations [69]. Another major drug-binding protein, α_1-acid glycoprotein, is an acute-phase reactant and mainly binds cationic drugs such as lidocaine, propranolol, muscle relaxants, and some opioids [68]. It increases by two-fold or greater, in contrast to albumin, and decreases the free fraction of drugs. Due to these cumulative changes, the doses for drugs usually have to be adjusted upwards during the hypermetabolic phase.

6. Non-pharmacologic techniques in burn pain management

As a means to prioritize a multi-disciplinary regimen in managing BIP, many non-pharmacologic approaches have been studied as adjunctive agents. The main novel techniques include virtual reality, distraction therapy, hypnosis, and cognitive behavioral therapy. Virtual reality has shown significance in procedural pain control because it distracts patients' attention into a virtual world of video games and three-dimensional features, which leaves less attention to process neural signals from pain receptors [70]. This is of particular importance because procedural pain is the greatest source of pain in burn populations. Burn patients report a 35–50 % reduction in pain while engaging in a distracting virtual reality activity and fMRI scans show reductions in pain-associated brain activity. Beyond pain control, virtual reality has been shown to reduce anxiety and stress during dressing changes, physical rehabilitation, and physiotherapy with few side effects [71]. Hypnosis has also shown some promise in the reduction of procedural pain and anxiety since hypnotherapeutic techniques utilize a feeling of relaxation [72]. These techniques, although proven to be efficacious, cannot be applied in all clinical settings and are often not available at all healthcare facilities. Other more widely available techniques include physiotherapy and cognitive behavior therapy by psychologists which are part of a multi-disciplinary team approach. This type of approach in conjunction with a multimodal analgesia regimen has the potential to significantly reduce anxiety and procedural pain in burn patients.

7. Conclusions

The management of BIP poses a significant challenge for clinicians due to its dynamic and variable nature that can stem from the various phases of burn injury, particularly the procedural phase in which patients experience immense pain from the therapies intended to treat burn injuries. It is also considered a foundational component of burn care due to the adverse effects that patients can experience from inadequate pain control. Even though opioids continue to be upheld as the mainstay of treatment, a multimodal pain management regimen with other non-pharmacologic adjunctive agents is of utmost importance due to the multifaceted nature of BIP. This regimen should be all-encompassing and requires a thorough understanding of the anatomic, metabolic, and psychologic factors that encompass this type of pain. A diligent approach with close attention to these factors by the healthcare team can have a significant impact on the patient's journey from initial injury to the rehabilitation period and can substantially improve long-term outcomes. Future research could focus on non-opioid techniques to manage BIP. These would encompass the role of peripheral immune macrophages and their effects at the site of injury and at the dorsal root ganglion. As indicated previously, the studies on the role central immune microglia have barely scratched the surface. RNA sequencing of these glia cells could provide further insight into how certain genes are up and down regulated and how they could be manipulated to achieve non-opioid analgesia. The role of gut microbiome in exaggerated pain in being studied in other pain conditions, but microbiome in BIP is very important in view of the altered gut microbiome induced by the injury itself and by the use of anti-microbials extensively in the *peri*-operative period.

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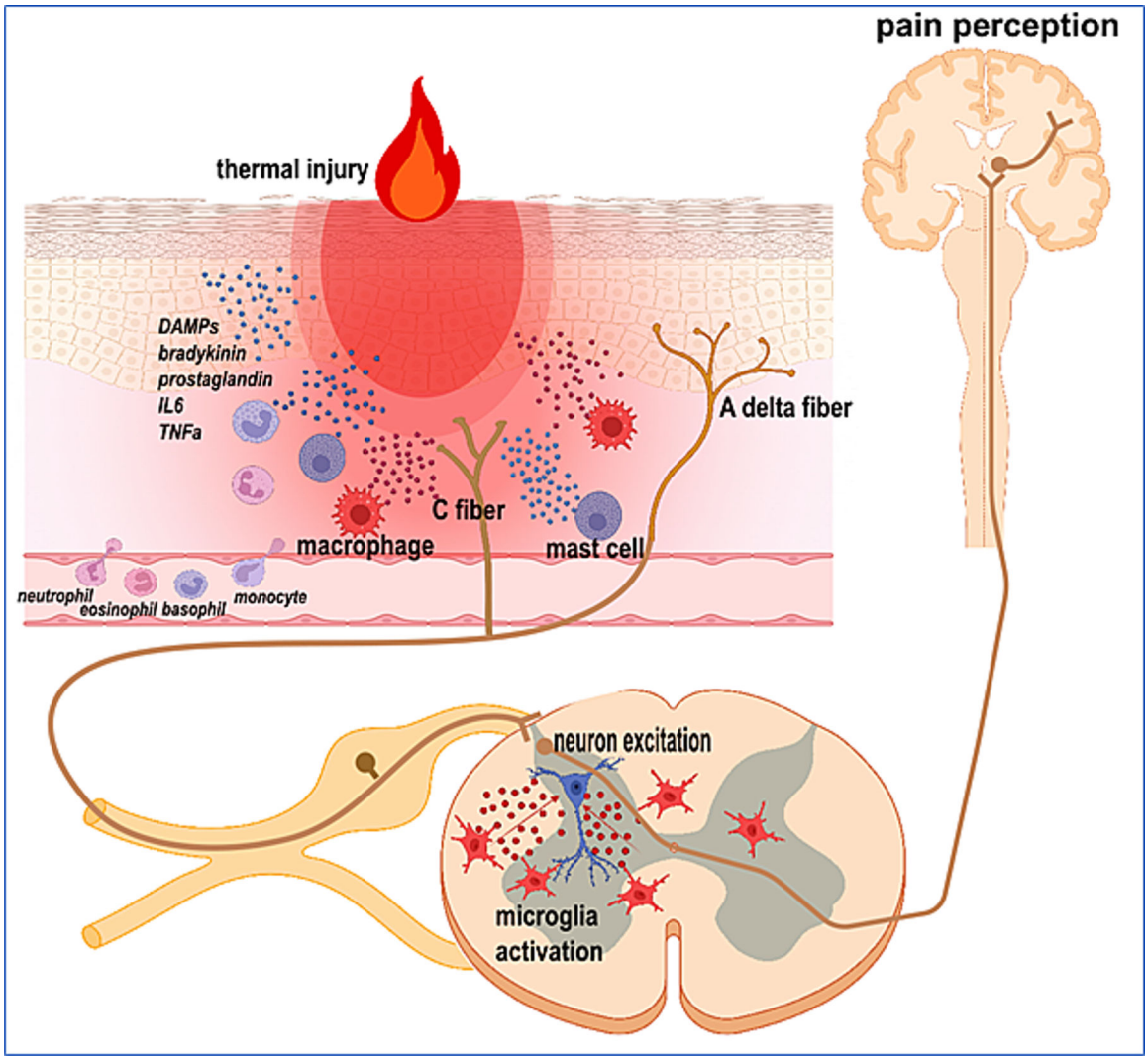

Fig. 1.

Burn injury-induced pain. Thermal injury to the skin initiates molecular and cellular responses resulting in pain. Nociceptors are activated immediately by heat. Burn injury causes cells to release DAMPs (e.g. ATP, protons) trigging a cascade release of histamine, bradykinin, catecholamines, prostaglandins, substance P, IL-6, TNFα, and IL-1β, etc., which sensitize the peripheral sensory nerves (e.g. C fiber and Aδ fiber) causing nociceptive pain. Burn-induced damage to peripheral nerves can trigger neuroinflammation in the spinal cord by activating microglia to producing inflammatory molecules which can directly cause neuron excitation leading to pain. The pain signals are eventually sent to brain for processing resulting in the perception of pain. DAMPs (damage-associated molecular patterns) are endogenous tissue breakdown products that mimic bacterial invasion and cause inflammatory responses by innate immune cells including macrophages and microglia. (Created with BioRender.com.)