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PAIN MANAGEMENT IN BURN INJURY

A A Gde Putra Semara Jaya,[1*] Anak Agung Ayu Anggreni,[2] Tjokorda Gde Agung Senapathi[3]

Abstract

Burn injury is one of the challenging cases in medical practice, which need comprehensive and multidiscipline management. Pain management is one of an important factors in caring for the burn patient. Pain management in burn injury is challenging and the patient may be at risk for undertreatment. Undertreated severe acute pain can lead to adverse consequences of many organ systems, delay recovery and discharge process, and potentially lead to chronic pain. Reports of inadequate pain relief persist, although there are advances in the acute pain management in recent years.

An understanding of pain pathway can achieve effective burn injury pain management, types of pain in burn injury, analgesics selection, continuous and accurate assessment of the pain and the response to therapy, dose adjustment to achieve maximum effect and minimal side effect, and role of nonpharmacological treatment as a complement to medication. Acute pain service plays an important role in providing effective burn injury pain management for reducing morbidity and mortality.

Keywords: *burn injury, burn injury pain, pain management*
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[1]Anesthesiologist, Department of Anesthesiology and Intensive Care, Mangusada Hospital, Badung, Bali, Indonesia
[2]General Practitioner, Emergency Department, Mangusada Hospital, Badung, Bali, Indonesia
[3]Anesthesiologist, Regional Anesthesia Consultant, Department of Anesthesiology and Intensive Care, Sanglah Hospital, Faculty of Medicine Udayana University, Denpasar, Bali, Indonesia

[*]Correspondence to:
A A Gde Putra Semara Jaya, Department of Anesthesiology and Intensive Care, Mangusada Hospital, Raya Kapal Street, 80351, Badung, Bali, Indonesia
gungthey84@yahoo.com

INTRODUCTION

Burn injury is one of the challenging cases in medical practice, which need comprehensive and multidiscipline management. Teamwork is the essence of burn injury management. No individual is capable of fulfilling the acute and long-term needs of the burn patient. Physicians, nurses, nutritionists, psychologists, physical therapists, and social workers can all participate as a team in the burn care. Burn injury management is best performed in the burn center.

Many aspects must be concerned in burn care, including evaluation of burn patients, initial management, fluid resuscitation, nutrition, the risk of infection, pain control, surgical management, wound care, and long-term care. Pain management is one of an important factors in caring for the burn patient. Pain management in burn injury is challenging and the patient may be at risk for undertreatment. Undertreated severe acute pain can lead to adverse consequences of many organ systems, delay recovery and discharge process, and potentially lead to chronic pain. Reports of inadequate pain relief persist, although there are advances in the acute pain management in recent years.[1-5] This review aims to provide a basic understanding of burn injury pain mechanism, type, and treatment.

The Depth of Burn Injury and Correlation to Pain

The depth of burn injury can be categorized into four degrees. First or superficial burn involves the epidermis only, erythematous, and painful. Second or partial thickness burn involves the entirety of the epidermis and a portion of the dermis. Based on the depth of dermal injury, partial thickness burns are further divided into superficial and deep partial thickness. Superficial partial thickness burns are typically pink, moist, and painful to the touch. Deep partial thickness burns are typically dry, mottled pink and white, and have variable sensation. Third or full thickness burns involve the epidermis and the entirety of the dermis, brown-black, leathery, and little or no pain.[4]

As described above, depth of burn injury determines the degree of burn injury pain. The most painful burn injury pain is first or superficial burn injury, followed by second or partial thickness burn injury. Third or full thickness burn injury associated with little or no pain. In addition to the depth of burn injury, the extent of burn also determines the degree of burn injury pain.

Mechanism of Burn Injury Pain

Mechanism of burn injury pain is complex, involving both peripheral and central processes. It combines features of nociceptive, inflammatory, and neuropathic burn injury pain. However, burn injury pain is subjective and different from each other by etiology, the depth, and extent of burn injury.[3,6]

Nociceptive pain. Initial burn injury pain is somatic nociceptive pain. Somatic nociceptive pain

is well-localized and usually described as a sharp, aching, tearing, or throbbing pain. Nociceptive pain ends when there is no more noxious stimulus on sensory nerve endings.[5,6]

Damaged tissue or potentially damaging (noxious) stimulus will stimulate sensory nerve endings called nociceptor. Nociceptor can be found in the soft tissue such as skin, subcutaneous tissue and muscles (somatic nociceptor), and in the viscera (visceral nociceptor). Nociceptors are the peripheral endings of A-delta (Aδ) and C sensory fibers.[5,6]

Noxious stimuli are transduced into an electrical signal by nociceptors and transmitted to secondary afferent neurons in the dorsal horn of the spinal cord. There are complex interactions between afferent neurons, interneurons and descending modulatory (inhibition) pathways in the dorsal horn. Second-order neurons, the spinothalamic tract and spinoreticular tract transmit a nociceptive signal to higher centers in the brain, i.e. thalamus, reticular formation, nucleus raphe magnus, and periaqueductal grey matter. Third-order neurons send signals to the somatosensory area I in postcentral gyrus and somatosensory area II in superior wall of Sylvian fissure. These brain cortices are responsible for perception and localization of pain.[5,6]

Inflammatory pain. Acute inflammatory response to burn injury causes inflammatory-triggered burn injury pain. The inflammatory response can be restricted to the site of injury or involve systemic processes, which can affect multiple organs and associated with significant morbidity and mortality.[3,7]

Activation of damage associated molecular pattern (DAMP) receptors and local ischemia or reperfusion injury in burn patients will lead to activation of the alternative complement pathway, the release of histamine, bradykinin, pro-inflammatory cytokine (TNF-a, IL-1b, IL-6), catecholamines, oxygen free radicals, nitric oxide, arachidonic acid cascade products, and the activation and recruitment of leukocytes.[3,7-9]

Released inflammatory and chemical mediators, vascular damage due to histamine release, and ischemia will generate sensitization and excitation of nociceptors, evoke sensitization of central neurons as a result of sustained nociceptive stimulation during and after injury. Inflammatory mediators and cytokine have a role in burn-induced allodynia and hyperalgesia.[3,7-9]

Neuropathic pain. Neuropathic pain may be caused by a combination of the peripheral, central and psychological mechanism. Damage of somatosensory system in burn injury lead to acute and chronic neuropathic pain. This damage generates ectopic firing and other pathological processes. Patients often describe the sensation of burning, pins and needles, shooting, stabbing sensations. There may be hyperalgesia (an increased pain to a painful stimulus) and allodynia (pain due to a normally innocuous stimulus). Neuropathic pain after burn injury could be exacerbated by light touch, dependent position, temperature change, and weight-bearing activities.[3,10,11]

Peripheral mechanisms of neuropathic pain include spontaneous firing, sensitization of nociceptor to stimuli, and up-regulation of an adrenergic receptor. Central mechanism apparently plays a major role in neuropathic pain. There are several phenomena involved in central sensitization including wind-up of wide dynamic range (WDR) neurons, microglial activation in the spinal cord, spinal sensitization by activation of the N-methyl-D-aspartate (NDA) glutamate receptor, loss of segmental inhibition, and reorganization of neural connections. The systemic activation of DAMP receptors, direct effects of C5a and a pro-inflammatory cytokine, causing increased blood-brain barrier permeability and may lead to central inflammation.[3,6]

Type of Burn Injury Pain

- Initial burn injury pain is nociceptive pain, immediate, severe, and regressive. It ends when there is no more noxious stimulus.
- Background burn injury pain is inflammatory pain, present on a daily basis, slightly varied between procedures, and prolonged until the wound healed.
- Procedural burn injury pain is nociceptive pain, immediate, severe, and repetitive, short to medium duration, which occurs during daily wound care (dressing changes), bath, and physiotherapy.
- Acute neuropathic burn injury pain is neuropathic pain during healing period.
- Chronic burn injury pain following healing of a burn injury. It may occur with an incidence of 25-36% and correlated with the severity of initial burn injury.
- Breakthrough burn injury pain is episodes of intense and sudden pain during rest. It may occur during or following healing period, with or without a trigger.[3,4,12,13]

Burn Injury Pain Treatment

Burn injury pain management is done to facilitate the effective and safe pain management, reduce the risk of complication or side effect, maintain the patient's functional abilities (includes

physical and psychologic), and enhance the quality of the patient's life. It involves pharmacological and nonpharmacological treatment.

The World Federation of Societies of Anesthesiologists (WFSA) has developed descending analgesic ladder to treat acute pain. This concept can be used in the management of acute burn injury pain. Initial severe acute burn injury pain is treated with a strong opioid, regional analgesia using local anesthetic, and peripherally acting drugs. Acute burn injury pain should decrease with time, the need of injection to deliver analgesic should cease and weak oral opioid can be established. The second rung involves the use of a combination of weak oral opioid and peripherally acting drugs. The final step, pain controlled by peripherally acting drugs alone, including aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs).[14,15]

The key to successful pharmacological treatment is the concept of multimodal analgesia which utilizes the dose adjustment to achieve maximum effect and decrease the risk of adverse reaction; and the continuous and accurate assessment of the patient's pain and the response to therapy.[5,16,17]

Nonpharmacological treatment is complementary to medication to control pain in burn injury patients. Its role cannot be underestimated. The treatment involves several disciplines, including psychologists, psychotherapists, physiotherapists, and pain specialists. It begins as early as possible to control the development of anxiety, which can aggravate pain.[3,16,17]

Initial burn injury pain. Initial burn injury pain is nociceptive pain. It can be reduced by cooling the burn. Strong and shorter acting analgesics are probably best for injury burn injury pain regarding its nature. Initial severe acute burn injury pain is treated with a strong opioid, regional analgesia using local anesthetics, and peripherally acting drugs. The drug options are similar to procedural burn injury pain as described later.[16]

Background burn injury pain. Background burn injury pain is inflammatory pain that continues while patients at rest. This type of pain is best treated with longer-acting agents. Based on the pathophysiology of background burn injury pain, regular evaluation and titration of multimodal analgesia are recommended. Combination of long-acting opioid, NSAIDs, acetaminophen (paracetamol), or ketamine infusion can be used.[3,4,16]

Intravenous opioid infusion, with or without patient-controlled analgesia (PCA), oral methadone, or oral prolonged released opioids (morphine or oxycodone) are opioids suitable for management of background burn injury pain. Methadone has a half-life of 6 hours and requires a taper to discontinuation. Opioids adverse effects are well-known, particularly sedation, respiratory depression, nausea, vomiting, itching, and constipation. Prolonged use of opioids increases the risk of tolerance or opioid-induced hyperalgesia. Tolerance will lead to increased dose requirement over time to achieve the same level of analgesia. Consider opioid-induced hyperalgesia if pain poorly controlled and worsen during opioid treatment.[4,17]

NSAIDs may reduce the dose of opiates needed by up to 20-30%, therefore may also reduce the adverse effects of opioids. NSAIDs act synergistically with opioids, but weak if used alone. NSAIDs can be classified by its action on the cyclooxygenase (COX) enzymes and chemical structure as traditional, nonselective COX inhibitors or selective COX-2 inhibitors. NSAIDs inhibit the formation of prostaglandins. COX-1 inhibition will lead to gastric ulcer and inhibition of platelet aggregation. Selective COX-2 inhibitors cause less bleeding and fewer ulcers than nonselective NSAIDs because it has little effect on COX-1. NSAIDs, especially selective COX-2 inhibitors associated with an increased risk of cardiovascular events. Severe burn injury, surgical excision, and grafting are at risk of bleeding.[4,16,17]

Paracetamol is an antipyretic and analgesic. The exact mechanism of action of paracetamol remains to be determined and is likely to involve several pain pathways, including effects on prostaglandin production, and on serotonergic, opioid, nitric oxide (NO), and cannabinoid pathways. Paracetamol is generally considered to have opioid-sparing effects (reduction in opioid consumption). Hepatotoxicity may occur with doses within the therapeutic range in patients with glutathione deficiencies, inadequate nutrition, P450 enzyme induction by chronic alcohol excess, or concomitant use of other drugs.[17,18]

Ketamine has been demonstrated to be an NMDA receptor antagonist, which may reduce central sensitization. Use of ketamine is limited by its psychotomimetic effects, including delirium, agitation, and hallucinations. Even subanesthetic dose of ketamine may cause hallucination. The incidence of psychomimetic symptoms is much lower in children than in adults. Co-administration with a benzodiazepine can reduce these effects.[3,4]

Procedural burn injury pain. Procedural burn injury pain is nociceptive pain. Strong and shorter acting analgesics are recommended for procedural burn injury pain. Procedural burn injury pain can be managed by combinations of short-acting opioids, subanesthetic doses of nitrous oxide/oxygen, ketamine, an alpha-2 agonist, or benzodiazepines. Nonpharmacological treatment includes hypnosis and virtual reality can be used while undergoing procedural interventions. Pain during rehabilitation can be relieved by relaxation, distraction, and cognitive-behavioral therapy.[3,4,16,17]

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A short-acting parenteral opioid is the drug of choice in procedural burn injury pain. Morphine, fentanyl, or oxycodone can be used. Remifentanil has an ultra-rapid onset of action and plasma metabolism. Remifentanil is administered as a continuous infusion during procedures. Fentanyl and alfentanil give an advantage of residual analgesia. The physician should be alert to the risk of sedation, respiratory depression, nausea, and vomiting.[3,17]

Nitrous oxide is an inhaled anesthetic with analgesic properties. Combination of inhaled nitrous oxide and oxygen can be used for short procedures as it has a rapid onset (within seconds) and short duration of action. Nitrous oxide may cause nausea and vomiting. Chronic use of nitrous oxide may lead to blood dyscrasias and neurological deficits due to inactivation of vitamin B_{12}.[3]

Ketamine is an intravenous anesthetic with potent analgesic effects at subanesthetic doses. The intravenous or intramuscular administration is generally selected for procedural burn injury pain, with a fast onset of action (1–5 minutes) and short duration of action (10–30 minutes). It induces a dissociative state, where patients appear conscious (e.g. eye-opening, swallowing) but unable to respond to sensory input. Rapid intravenous bolus administration or combination with opioids may produce apnea. The anticholinergic agent can be used to reduce hypersalivation associated with ketamine. Upon recovery, patients can experience psychotomimetic effects. Deep conscious sedation can be achieved by combination of ketamine with propofol or midazolam.[3,17]

Alpha-2 agonists is an analgesic by stimulating the descending inhibitory pain pathways. They have sedative and antihypertensive effects. Dexmedetomidine is a highly selective α2-adrenoceptor agonist. It is eight times more selective for the α2-adrenoceptor than clonidine. Dexmedetomidine has a shorter duration of action than clonidine. Hypotension and bradycardia are the most common adverse effects of alpha-2 agonist.[17]

Benzodiazepine is an anesthetic agent and not considered analgesic. It can relieve pain in combination with other analgesics, most likely due to their sedative, hypnotic, and anxiolytic effects. Anxiety can cause decreased pain tolerance and exacerbate pain symptoms. Midazolam is the most commonly used due to the rapid onset of action and relatively rapid recovery. Diazepam and lorazepam have prolonged the context-sensitive half-time. Benzodiazepines have synergistic sedative effect with another central nervous system depressant including opioids, intravenous anesthetics, and alpha-2 agonists.[3,4,17]

Hypnosis is an altered state of consciousness. It is characterized by increased receptivity to suggestion, ability to change perceptions and sensations, and increased capacity for dissociation. Virtual reality is a method of distraction. The technology isolates the patients from the real world. The patients are actively engaged in another task in a virtual environment while undergoing procedural interventions.[3,17]

Acute neuropathic burn injury pain. Neuropathic burn injury pain can occur acutely. It can present only at the time of injury and may become chronic following healing of the burn injury. This phenomenon correlates with extensive damage to cutaneous nociceptors and conducting nerve fibers in burn wound. Pregabalin is effective to relieve acute neuropathic symptoms. Some burn centers use tricyclic antidepressants and other anticonvulsants. Tramadol and opioids also promote a beneficial effect in neuropathic pain.[3,17]

Chronic burn injury pain. Basic principles of chronic pain management should be applied including multimodal analgesia, nonpharmacological treatment, and multidisciplinary team. Chronic neuropathic burn injury pain is difficult to treat using conventional analgesics. Pregabalin, gabapentin, antidepressant, and steroid injection are reportedly effective in some patients with neuropathic pain symptoms. Nonpharmacologic treatment by rest, elevation, compression garment use, and massage may reduce pain symptoms.[3,11,16]

Pregabalin and gabapentin are anticonvulsant. Anticonvulsant acts by blocking voltage-gated calcium or sodium channel and suppress spontaneous neural firing, thus diminish the central sensitization in chronic pain. Pregabalin was well-tolerated and significantly reducing neuropathic pain in burn injury patients.[6,17]

Antidepressants demonstrate an analgesic effect at a dose lower than required for the antidepressant effect. They activate the descending inhibitory pathways in the spinal cord. Antidepressants potentiate the opioids action. Low dose amitriptyline is useful to relieve chronic burn injury pain. Selective serotonin reuptake inhibitors may also be used as an alternative to a tricyclic antidepressant. The analgesic effect of antidepressants usually occurs within days or weeks.[6,17]

Breakthrough pain. It can happen during or following healing period can be treated by "rescue medication." The analgesic used is working fast and lasts for a short period. Severe breakthrough pain is commonly treated with a short-acting opioid that is 5-20 percent of total daily opioid dose to manage chronic pain.[3,16,17]

Acute Pain Service

Acute pain service (APS) is an organization in the hospital, dedicated to the management of acute pain including in perioperative setting, parturient, trauma, acute medical condition, and other patients with acute pain. The APS has the responsibility for 24h pain management including regular pain assessment, adjustable pain management delivery, complications or side effects assessment and management, documentation of records, audits and defined performance criteria for evaluation. The APS also has an important role to ensure the safety of the techniques, continuous professional development, provides in-house training programs for medical and nursing staff about the identification and management of complications, patient education about pain and treatment options, committed to audits of the efficacy of the methods and cost-effectiveness.[5,19,20]

The APS has a lot of treatment and technique modalities, from pharmacological, interventional, and nonpharmacological methods. Pharmacological modalities by using opiates, NSAIDs, aspirin or acetaminophen and adjuvants. Various technique can be used including patient-controlled analgesia (PCA), epidural or intrathecal analgesia, and peripheral nerve blocks.[5,19,20]

The characteristic of APS as described above are suitable for burn injury pain management. The APS plays an important role in the success of burn injury pain management using various treatment and technique modalities, regular pain assessment and response to therapy, continuous analgesics adjustment, assessment and management of complication or side effect.

CONCLUSION

Pain management in burn injury is challenging. An understanding of pain pathway can achieve effective burn injury pain management, types of pain in burn injury, analgesics selection, continuous and accurate assessment of the pain and the response to therapy, dose adjustment to achieve maximum effect and minimal side effect, and role of nonpharmacological treatment as a complement to medication. Acute pain service plays an important role in providing effective burn injury pain management for reducing morbidity and mortality.

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