

Burn Trauma: An Emerging Model for Acute Pain



Major advances have improved management of acute pain globally, but more than 50% of patients still have severe to intolerable pain after surgery or trauma (<http://www.efic.org/eap.htm>). Emphasis in acute pain studies has shifted to outcomes that go beyond “good pain relief” to reductions in the risk of developing chronic pain, acute medical conditions, and the development of psychological disturbances due to pain. In addition, practice in acute pain medicine now extends well beyond the management of post-operative pain and has advanced in numerous clinical situations including trauma, spinal cord injury, back pain, and more recently, burn pain. However, there is relatively little direction on the appropriate design and conduct of pain experienced in burn patients. This review will summarise design-important issues in burn pain management studies with an emphasis on the challenges in burn pain clinical trials.

Burns are a global public health problem, accounting for an estimated 265,000 deaths annually (<http://www.who.int/mediacentre/burns>). Non-fatal burns are a leading cause of morbidity, including prolonged hospitalisation, disfigurement and disability. Moreover, burns and their subsequent injury and trauma are among the leading causes of disability-adjusted life-years (DALYs) lost in low- and middle-income countries. Burn injury causes pain and damage to the skin and underlying tissues and has been classified into three groups based on vertical spreading: First-degree burns affecting epidermis, second-degree burns involving epidermis and part of dermis, and third-degree destroying epidermis and dermis (Kao *et al.*, 2000). Burn pain management is typically based upon clinical experience and physician and/or institutional preference, since available evidence is insufficient to clearly support one approach. There are many variables that affect burn pain: the phase of the wound and degree of the burn, the person affected (i.e. respiratory and haematological effects need to be considered for pain treatment of infants or young children), depth of the skin lesion and the inflammatory response (Richardson and Mustard, 2009). Therefore, considering the pain to be homogeneous among all patient phenotypes leads to inadequate pain assessment which hinders meaningful research and prevents optimal management of burn pain.

Opioids, anti-depressants, anti-convulsants and anti-inflammatory drugs are the major analgesics used to control pain (Latarjet and Choinere, 1995). Burn wounds are managed with surgery, autografts, topical dressings, corticosteroids, laser therapy and topical therapeutic agents including silver sulfadiazine (Fraser *et al.*, 2004). Despite the availability of these treatments, and continued research in the field, the clinical outcomes for burn patients are generally not satisfactory. For instance, the major concern with chronic use of most analgesics is their side-effects, which include addiction and adverse

effects on various organ systems (Janecka *et al.*, 2010). An additional concern about opioid analgesics is that, even though they represent the best approach to burn pain, and are highly effective for treating background pain, their analgesic efficacy for extreme procedural pain is limited. Patients with severe burns routinely experience severe pain during wound care, despite aggressive pain control with potent opioid analgesics (Patterson *et al.*, 2004). As a result, the search continues to identify therapies with reduced side-effects to treat both acute and chronic pain following burn injury.

Subject characteristics that affect burn wound healing include age, nutritional status, underlying medical conditions, concomitant injury (e.g., head trauma, inhalation injury, bone fractures), and scores that represent an overall severity of illness or injury (e.g., the American Society of Anesthesiologists (ASA) Classification, the Trauma-Injury Severity Score (TRISS), or the Acute Physiology and Chronic Health Evaluation (APACHE) III score) (FDA.gov). Patients with serious burns commonly receive multiple concomitant treatments, making it sometimes difficult to detect a treatment effect. For this reason, stratification by injury severity and other potentially confounding factors that are clinically significant and discussed above should be considered to minimise imbalances among treatment groups. A multidisciplinary approach is crucial for a successful clinical outcome and therefore must consider all of the above variables in targeting the various different patient populations: cause of burn, phase and degree of burn, depth of skin lesion, and level of inflammatory response.

As recommended by the Food and Drug Administration, randomisation is particularly important for reducing bias in burn pain indication trials because standard wound care procedures and baseline wound characteristics generally have a profound effect on outcome. Stratification by study centre is recommended to minimise any imbalances among study arms, considering the level of variation in standard wound care among clinical study sites. In addition, variables thought to significantly affect outcome should be incorporated into the planned efficacy analyses, even if these variables are not used for stratification in randomisation (FDA.gov).

Despite advances in burn care, control of burn pain is often inadequate during the acute and chronic rehabilitation phases of burn care (Retrouvey and Shahrokhi, 2015). Burn patients report intense pain during procedures such as wound debridement, dressing changes and strenuous physical and occupational therapy. In fact, procedural pain is the most common grievance reported by the burn population (de Jong *et al.*, 2007). Therefore, therapeutic options for better management of pain and anxiety during these procedures need to

be identified. Patients with burn wounds frequently require high doses of opioids and anxiolytic agents, to the extent that clinicians must weigh the risks associated with these doses against achieving adequate analgesia and comfort. The biggest risk is over-sedation causing breathing troubles. Inadequate pain control during these procedures heightens pain perception, anxiety, and fear surrounding the experience and may lead to patients experiencing additional psychological disorders like depression, acute stress disorder (ASD), and post-traumatic stress disorder (PTSD) (Askay and Patterson, 2008; Wiechman *et al.*, 2009). Primary outcome measures in procedural burn pain should include the amount of standard of care medications (opioid and anxiolytic agents) each group receives during their procedure; the presence of pain-related anxiety shortly after the procedures; blood markers of stress during the procedures; and the presence of depression, anxiety and stress disorders prior to discharge. Secondary measures can include patient-reported pain scores using the visual analogue scale when a subject is scheduled for a dressing change, and rating their pain using the VAS within 4-12 hours after the end of the procedure.

Standardising Outcome Measures to Guide Clinical Trials in Burn Patients

Burn pain amelioration endpoints should be accompanied by assessment instruments which are suitable to measure the type of pain for which the patient is experiencing (i.e. type of burn, phase of burn, etc). These studies should include, as safety endpoints, assessments of product effects on improved wound healing (i.e. incidence of complete wound closure, accelerated wound closure, facilitation of surgical wound closure, and/or quality of healing) as well as improved wound care (treatment of wound infection, debridement, and *wound pain*). Assessment scales are critical to understanding the level of the underlying burn pain syndromes and the effectiveness of each patient's treatment regime. As reviewed by Mahar and colleagues, 25 randomised clinical trials were identified utilising pain assessment tools. Unidimensional pain assessment tools were used most frequently, with multidimensional tools used less often, despite the multifaceted and complex nature of burn pain (Mahar *et al.*, 2012). The most common pain assessment tools in the burn population are verbal self-report instruments that measure pain intensity, such as the "0 to 10" numeric rating scale. However, visual analogue, face and colour scales are also used. Given the nature of this type of trauma, when patients are unable to provide a self-report, behavioural observations may be a valid approach (Herr *et al.*, 2006). Choinière and colleagues (1994) introduced a visual analogue scale designed to elicit a verbal self-report. In this study the validity and utility of the visual analogue thermometer (VAT) was assessed and compared with a conventional numeric (NUM) and adjective pain scale (ADJ) with a group of 103 burned patients and 51 nurses. Analyses of the results supported the concurrent and construct validity of the VAT as a pain measure. Furthermore, the



VAT gave more sensitive and precise pain measures than the ADJ and/or NUM scales. No major difference between the three scales emerged in the patients' preference. The same was true for the nurses' evaluation except for those who had more clinical experience with the VAT and who tended to prefer this scale for its accuracy and ease of utilisation. However, similar to depression clinical studies, significant discordance has been demonstrated between the nurses or personnel observing and burn-injured patients' pain assessments (Choinière *et al.*, 1990; Geisser *et al.*, 1995). For example, patients' and nurses' ratings of pain and tension were obtained during 107 burn dressing changes among 11 burned patients and although both nurses' and patients' ratings of pain were positively related to amount of analgesic medications administered, amounts were inversely related to patients' reports of pain in a subsample of dressing changes in which anxiolytics were administered (Geisser *et al.*, 1995). For this reason, individuals who are unable to communicate their pain are at greater risk for undertreatment of their pain. Taken together, educating the patient as to the purpose and importance of multiple

pain assessments and offering them a choice as to which method they prefer may provide them with some control over communication methods as well as improve the capacity of more patients to participate in research.

Recommendations for New Methodology in Research

Burn care is an area which has advanced persistently over the past years with improved survival and quality of survival. However, the translation of what we know into clinical practice remains complex with the numerous operational and methodological challenges faced when designing a rigorous clinical trial that addresses the physiological and psychological aspects of burn injury associated with pain management. The injury results in physical and psychological sequelae such that every intervention from the point of injury will influence each patients' recovery. Mental and physical recovery is affected by numerous variables such as first aid, wound cleaning, prehospital care, pain management, resuscitation, surgery, wound care, nutrition, scar management, and functional and psychological rehabilitation. Clearly the clinical problem faced on a daily basis is complex and research is essential in continuing to developing innovative solutions to solve the clinical problems. Thus, a comprehensive methodology for responder criteria would take into account three core aspects: pain, physical function and patient global assessment.

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