Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.elsevier.com/locate/burns

Review

Progress of clinical practice on the management of burn-associated pain: Lessons from animal models

Matthew K. McIntyre [a], *John L. Clifford* [a], *Christopher V. Maani* [b], *David M. Burmeister* [a,*]

[a] *United States Army Institute of Surgical Research, 3650 Chambers Pass, BHT1:Bldg 3610, JBSA Fort Sam Houston, TX 78234-6315, United States*
[b] *Brooke Army Medical Center, Department of Anesthesia and Operative Services, San Antonio Uniformed Services Health Education Consortium (SAUSHEC) Anesthesia Residency Program, 3551 Roger Brooke Drive, JBSA Fort Sam Houston, TX 78234-6315, United States*

ARTICLE INFO

Article history:
Accepted 21 January 2016

Keywords:
Burn pain
Animal models
Hyperalgesia
Allodynia
Analgesia

ABSTRACT

Opioid-based analgesics provide the mainstay for attenuating burn pain, but they have a myriad of side effects including respiratory depression, nausea, impaired gastrointestinal motility, sedation, dependence, physiologic tolerance, and opioid-induced hyperalgesia. To test and develop novel analgesics, validated burn-relevant animal models of pain are indispensable. Herein we review such animal models, which are mostly limited to rodent models of burn-induced, inflammatory, and neuropathic pain. The latter two are pain syndromes that provide insight into the pain caused by systemic pro-inflammatory cytokines and direct injury to nerves (e.g., after severe burn), respectively. To date, no single animal model optimally mimics the complex pathophysiology and pain that a human burn patient experiences. No currently available burn-pain model examines effects of pharmacological intervention on wound healing. As cornerstones of pain and wound healing, pro-inflammatory mediators may be utilized for insight into both processes. Moreover, common clinical concerns such as systemic inflammatory response syndrome and multiple organ dysfunction remain unaddressed. For development of analgesics, these aberrations can significantly alter the potential efficacy and/or adverse effects of a prescribed analgesic following burn trauma. We therefore suggest that a multi-model strategy would be the most clinically relevant when evaluating novel analgesics for use in burn patients.

Published by Elsevier Ltd and ISBI

* *Corresponding author*. Tel.: +1 210 539 9226; fax: +1 210 539 6244.
E-mail addresses: Matthew.k.mcintyre3.vol@mail.mil (M.K. McIntyre), John.l.clifford11.civ@mail.mil (J.L. Clifford), Christopher.v.maani.civ@mail.mil (C.V. Maani), David.m.burmeister3.civ@mail.mil (D.M. Burmeister).

Abbreviations: CFA, complete Freund's adjuvant; FTB, full thickness burn; GFR, glomerular filtration rate; LA, local anesthetics; NMDA, N-methyl-D-aspartic acid; OIH, opioid-induced hyperalgesia; PK, pharmacokinetics; PD, pharmacodynamics; PTSD, post-traumatic stress disorder; SIRS, systemic inflammatory response syndrome; SIN, sciatic inflammatory neuritis; SNL, spinal nerve ligation; TBSA, total body surface area; USAISR, US Army Institute of Surgical Research.

http://dx.doi.org/10.1016/j.burns.2016.01.023
0305-4179/Published by Elsevier Ltd and ISBI

Contents

1. Introduction

Burns represent a major public health concern and burden to the healthcare system due to significant morbidity and mortality. The annual cost of the treatment of burn patients in the US is estimated at more than $573 million [1] and the mean cost for each pediatric patient is $83,535 [2,3]. However this figure can exceed several hundred thousand dollars and does not include outpatient costs such as continued rehabilitation, behavioral health support, or other quality of life indices [4,5]. Inadequate control of severe burn pain, as with other types of trauma, may result in delaying the discharge of burn patients from treatment centers [6,7].

Early and aggressive attenuation of pain is not only important for keeping the patient comfortable throughout the wound healing process, but it is also necessary for increased quality of life years after recovery [8]. Post-traumatic stress disorder (PTSD) may develop in burn patients and can become chronic. In line with this, a retrospective cohort study showed that pain levels were positively correlated with PTSD survey scores but not with injury severity scores, suggesting that early acute pain is related to PTSD symptoms [9]. Additionally, other acute symptoms such as depression, anxiety, and insomnia also appear to affect chronicity of burn pain [10,11]. In fact, the pain experienced by burn victims at discharge is indicative of long-term suicidal ideation [12]. Moreover, in a study examining 358 patients with an average of 12 years between burn and survey response, 52% claimed to have ongoing burn-related pain, 66% reported that pain interfered with their rehab and 55% felt that it interfered with their daily lives [13].

Therefore, the acute and chronic pain experienced by burn patients remains a significant challenge for patients and clinicians alike, with a demonstrated need for high quality research to guide and improve therapeutic options. Moreover, the pain experienced by burn patients often evolves from time of injury through recovery, and the development of targeted analgesics for each stage of burn care is needed as a means of reducing cost and improving quality of life. Various pre-clinical animal models will prove to be invaluable tools to develop novel analgesics for targeting these different stages of pain. The advantages and disadvantages of modeling pain in animals are discussed below, with an emphasis on gaps and shortcomings concerning burn-associated pain.

1.1. *Classifications of burn pain*

Pain experienced during recovery from burn wounds can be broken into four classes; wound (initial injury), procedural, background, and breakthrough pain; wherein each should receive separate assessment in terms of analgesic need. Wound and procedural pain, the most severe types of burn pain, can be elicited by manipulation of affected tissue (e.g., debridement, dressing changes, physical therapy, baths, removal of skin graft staples), and can include the donor site of a skin graft. Preemptive pain management usually consists of short-acting opioid analgesics, but may also include sedatives, anxiolytics (e.g., propofol, benzodiazepines), lidocaine or other non-opioid analgesics, as delineated in Table 1 [14–16]. The goal of this treatment regimen is to reduce burn-associated pain, anxiety, and distress typically associated with

Table 1 – Analgesics commonly used in burn patients. Opioids, non-opioids, and non-pharmacological methods can be used alone or in combination for analgesia.

Weak opioids	Strong opioids	Non-opioids	Non-pharmacologics
Tramadol	Morphine	NSAIDs	Virtual reality
Meperidine	Fentanyl	Paracetamol/APAP	Acupuncture
	Methadone	Lidocaine/LA's	Acupressure
	Hydromorphone	Ketamine	Hypnosis
	Piritramide	Gabapentin	
	Oxycodone	Benzodiazepines	
	Remifentanil	Anxiolytics	

Please cite this article in press as: McIntyre MK, et al. Progress of clinical practice on the management of burn-associated pain: Lessons from animal models. Burns (2016), http://dx.doi.org/10.1016/j.burns.2016.01.023