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Research Article

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Prevalence and associated predictors for patients developing chronic neuropathic pain following burns

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Abstract

Background: Chronic pain, unrelated to the burn itself, can manifest as a long-term complication in patients sustaining burn injuries. The purpose of this study was to determine the prevalence of chronic neuropathic pain (CNP) and compare burn characteristics between patients who developed CNP and patients without CNP who were treated at a burn center.

Methods: A single-center, retrospective analysis of 1880 patients admitted to the adult burn center was performed from 1 January 2014 to 1 January 2019. Patients included were over the age of 15 years, sustained a burn injury and were admitted to the burn center. CNP was diagnosed clinically following burn injury. Patients were excluded from the definition of CNP if their pain was due to an underlying illness or medication. Comparisons between patients admitted to the burn center with no pain and patients admitted to the burn center who developed CNP were performed.

Results: One hundred and thirteen of the 1880 burn patients developed CNP as a direct result of burn injury over 5 years with a prevalence of 6.01%. Patients who developed CNP were a significantly older median age (54 years vs. 46 years, $p = 0.002$), abused alcohol (29% vs. 8%, $p < 0.001$), abused substances (31% vs. 9%, $p < 0.001$), were current daily smokers (73% vs. 33%, $p < 0.001$), suffered more full-thickness burns (58% vs. 43%, $p < 0.001$), greater median percent of total body surface area (%TBSA) burns (6 vs. 3.5, $p < 0.001$), were more often intubated on mechanical ventilation (33% vs. 14%, $p < 0.001$), greater median number of surgeries (2 vs. 0, $p < 0.001$) and longer median hospital length of stay (LOS) (10 days vs. 3 days, $p < 0.001$), compared to those who did not develop CNP, respectively. Median patient follow-up was 27 months.

Conclusions: The prevalence of CNP over 5 years was 6.01% in the burn center. Older ages, alcohol abuse, substance abuse, current daily smoking, greater percent of total body surface area (%TBSA) burns, third degree burns, being intubated on mechanical ventilation, having more surgeries and longer hospital LOS were associated with developing CNP following burn injury, compared to patients who did not develop CNP following burn injury.

Key words: Alcohol, Burns, Chronic pain, Length of stay, Nerve, Neuralgia, Prevalence, Smoking, Substance, Surgery

Background

The development of chronic pain, unrelated to the initial burn itself, can result following burn injury. This pain can contribute to decreased quality of life (QOL) and long-term patient morbidity, limiting functional recovery [1–6]. The reported prevalence of chronic neuropathic pain (CNP) following burns within the last 10 years ranges from 7.3% to 18% [7, 8]. CNP develops after partial or complete peripheral nerve injury [1, 9–18]. These injuries may manifest as mononeuropathy (abnormality in a single peripheral nerve distribution), multiple mononeuropathies (mononeuropathy multiplex, simultaneous abnormalities of two or more peripheral nerves in separate areas of the body) and/or polyneuropathy (abnormality in many nerves in a distal symmetrical pattern) [19].

Mononeuropathy results from localized traumas that include the direct burn injury, surgical injury from debridement, escharotomies, fasciotomies, compression from tight dressings, edema, eschars, heterotopic ossification (HO), incorrect splinting and forceful physical therapy [20–22]. Mononeuropathy multiplex results from combinations of localized and generalized trauma, and crush injuries to multiple areas [20]. Polyneuropathy can be categorized as generalized polyneuropathy or polyneuropathy of critical care illness [1]. Polyneuropathy results from combinations of generalized trauma—these include drugs, sepsis, neurotoxins and metabolic factors [20, 23, 24]. Polyneuropathy of critical care illness results from sepsis, multi-organ failure and prolonged mechanical ventilation [25, 26].

Burn scars have diminished sensory function compared to uninjured tissues [27]. Neurotransmitters are released from injured tissue during the wound healing process. Neurotransmitter release along with abnormal cutaneous innervation may contribute to CNP observed in burn patients [11, 28–31]. Experimental models have demonstrated an increased density of nociceptive A delta and C nerve fibers, with no difference in skin nerve density in burn scars compared to uninjured tissues [27, 28].

The variability of the prevalence of CNP did not provide a useful understanding in our population following burn injury [7, 8]. Knowing the true prevalence and associated predictors can aid clinicians in determining the risks of developing neuropathic pain as a chronic illness. The purpose of this study was to determine the prevalence and associated predictors for CNP in burn patients.

Methods

Study design

We performed an Institutional Review Board (IRB) approved retrospective medical record review to collect a cohort of patients admitted to the adult burn center from 1 January 2014 to 1 January 2019. This cohort has been previously evaluated using different study parameters (IRB00213320). The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines were adhered to throughout our review [32].

Study population

All patients included were older than 15 years of age, sustained a burn injury and were admitted to the burn center during the study period. The burn center consisted of the burn wound unit and burn intensive care unit (ICU). Patient lists were generated and each patient's electronic medical record was manually reviewed by the lead author.

We stratified patients into two groups for comparison. The first group of patients comprised of all patients admitted to the burn center with no progression to chronic pain (no-pain group), and the second group of patients developed CNP lasting greater than 6 months following the injury of burn (pain group). CNP was evaluated and diagnosed by at least two healthcare providers during follow-up visits (physician and physical therapist (PT) or occupational therapist (OT)) [33]. The pain group patients described pain as paresthesias and/or dysesthesias that included: shooting, stabbing, sharp, burning, tingling, numbness, dullness, throbbing, pruritus and intermittent and/or continuous sensations. All patients in the pain group were prescribed neuropathic medications—gabapentin (Neurontin®) or pregabalin (Lyrica®) were neuropathic medications trialed by all pain group patients. Patients were excluded from the pain group if they had pre-existing CNP due to an underlying illness or medication unrelated to the burn injury. Both groups were evaluated for differences and compared to determine what factors were associated predictors for developing CNP.

Outcomes analysed

The primary outcome was the prevalence of CNP in patients treated at the burn center over the 5-year period. Secondary outcomes included patient age, sex, alcohol abuse, substance abuse, current daily smokers, percent of total body surface area (%TBSA) burned, number of patients with full-thickness burns, intubation on mechanical ventilation, number of burn surgeries and hospital length of stay (LOS) in days. An outcome was considered if evaluated and documented by a minimum of a physician and PT or OT.

Statistical analysis

Medians, interquartile (IQR), odds ratios (OR) and 95% confidence intervals (95% CI) were used for descriptive statistics. Statistical analyses were performed to compare the no-pain group to pain group. We performed the Fisher's exact test for categorical variables and Mann–Whitney *U* test for continuous variables based on the nonparametric distribution of population data and disproportionate sizes of comparative groups. A sub-group analysis with stepwise binomial logistic regression using forward selection was performed to compare age, alcohol abuse, substance abuse, current daily smokers, %TBSA burned, number of patients with full-thickness

burns, intubation on mechanical ventilation, number of surgeries and hospital LOS between the two groups. Reciprocal transformation was implemented for continuous non-parametric variables; these included age, %TBSA, number of surgeries and hospital LOS. Outcomes of analyses were two-tailed, with a significance level set at $\alpha = 0.05$. All analyses were performed with SPSS Version 25.0 (IBM Corporation, Redmond, WA).

Results

Prevalence

The reported prevalence of CNP following burn injury ranges in the literature from 7.3% to 82%, spanning the years 1989 to 2013 [7, 8, 24, 34–40] (Table 1). Over the 5-year period, 1880 patients meeting eligibility criteria were admitted to the burn center and included in the study. One hundred and thirteen of the 1880 burn patients developed CNP. The prevalence of CNP was 6.01% in our population following burn injury.

Predictors of CNP following univariate analysis

One hundred and thirteen patients in the pain group were compared to 1767 patients in the no-pain group. Patients who developed CNP were significantly older (median [IQR] = 54 [39–62] years vs. median [IQR] = 46 [31–59] years, $p = 0.002$), abused alcohol (33/113 [29%] vs. 148/1767 [8%], $p < 0.001$), abused substances (35/113 [31%] vs. 163/1767 [9%], $p < 0.001$), were current daily smokers (83/113 [73%] vs. 585/1767 [33%], $p < 0.001$), suffered more full-thickness burns (66/113 [58%] vs. 755/1767 [43%], $p < 0.001$), had a greater %TBSA burned (median [IQR] = 6 [3–25] vs. median [IQR] = 3.5 [2–8], $p < 0.001$), were more often intubated on mechanical ventilation (37/113 [33%] vs. 239/1767 [14%], $p < 0.001$), had a greater number of surgeries (median [IQR] = 2 [1–6] vs. median [IQR] = 0 [0–1], $p < 0.001$) and had a longer hospital LOS (median [IQR] = 11 [5–30] days vs. median [IQR] = 3 [1–9] days, $p < 0.001$), compared to those who did not develop CNP. There were no significant differences between sexes for the development of CNP (Table 2). Median (IQR) patient follow-up was 27 (10–45) months.

Predictors of CNP following multivariate analysis

Following multivariate analysis, patients in the pain group were more likely to have comorbid alcohol abuse (OR = 2.04, 95% CI [1.06, 3.94]; $p = 0.030$), comorbid substance abuse (OR = 3.12, 95% CI [1.65, 5.93]; $p < 0.001$), be current daily smokers (OR = 6.91, 95% CI [3.72, 12.67]; $p < 0.001$), have had a greater number of surgeries (OR = 7.51, 95% CI [2.91, 19.21]; $p < 0.001$) and have had a longer hospital LOS (OR = 1.01, 95% CI [1.00, 1.02]; $p = 0.010$) than patients in the no-pain group (Table 3).

Discussion

We were able to compare all burn patients to burn patients who developed CNP over a 5-year period. We determined the 5-year prevalence and associated predictors for the development of CNP in the largest study performed to date. Our 6.01% prevalence of developing chronic, neuropathic pain following burns was less than the range of 7.3% to 18%, reported within the last 10 years [7, 8]. When including all studies in the literature, the prevalence of CNP following burn injury ranged from 7.3% to 82%, spanning the years 1989 to 2013 [7, 8, 24, 34–40]. Evaluating the methodology of all studies reporting prevalence individually, and chronologically, can help determine the discrepancies for each study's reported prevalence.

Four studies retrospectively distributed questionnaires to patients as long as 11 years following initial burn injury [7, 35, 37, 39]. Assessing patients over the phone or through mailed surveys, rather than evaluating them clinically, may have overestimated the prevalence of CNP. We were unable to differentiate the type of pain these patients were suffering and if the pain was directly attributed to the burn or a medication or illness. Two of the 4 studies had a 23% survey response rate and a high possibility of selection bias for those responding because of chronic pain [7, 37]. All these factors may explain the 82% prevalence of CNP observed by Choiniere *et al.* [35].

All 10 studies evaluated a population of less than 1000 patients, and 4 studies evaluated a population of less than 100 patients [24, 34, 38, 40]. Determining the prevalence of a condition is difficult with a small sample size. Calculations using small sample sizes may reduce the statistical power and overestimate study findings, resulting in a type II error. This may explain the differences in observed risk factors for CNP. Ward *et al.* found no associations with age, %TBSA or mechanism of burn, while Khedr *et al.* found associations with age, %TBSA and mechanism of burn [38, 40]. Both studies had sample sizes of less than 100 patients when determining population characteristics.

A misconception that has reoccurred in the literature is the use of electro-diagnostic studies (EDS) to diagnose pain. Pain is subjective, and EDS are not capable of differentiating pain from no pain, especially with small fiber neuropathies [33]. Four studies used EDS as a method for assessing CNP [8, 24, 36, 38]. Margherita *et al.* reported polyneuropathy determined using clinical examination and EDS [24]; patients that did not undergo EDS were excluded. However, polyneuropathy is a small fiber disease, undetectable using EDS [33]; therefore, patients should not have been excluded on this basis. The authors were detecting motor nerve neuropathies presenting with conduction delays.

The terms pain, neuropathic pain and CNP are often used synonymously, with little standardization in meaning [33]. We defined chronic pain as paresthesias and/or dysesthesias lasting greater than 6 months and requiring neuropathic medication. Defining CNP is important for any study assessing its prevalence. Malenfant *et al.* considered paresthesias

Table 1. Studies evaluating the prevalence of chronic neuropathic pain (CNP) after burn injury

Author	Publication year	Study design	Sample size	Study diagnosis of CNP	Prevalence of CNP	Study conclusions
Ward *et al.* [40]	1989	Retrospective	60	Clinical examination	25%	Prevalence was not due to age, %TBSA or mechanism of burn etiology. No associations were found for developing CNP.
Choiniere *et al.* [35]	1991	Retrospective	104	Contacting patients by phone and inquiring if they had CNP and if it was associated with the burn injury	82%	Prevalence was not due to age, sex or etiology. CNP was associated with burn size and skin grafting.
Margherita *et al.* [24]	1995	Prospective	17	Clinical examination and EDS	41%	Burn-associated peripheral neuropathy is associated with thermal injury and may be present as early as one week on EDS.
Malenfant *et al.* [39]	1996	Retrospective	288	Contacting patients to administer questionnaires and assess if they had CNP and it CNP was associated with the burn injury	36.4%	Prevalence was not due to age, sex, burn etiology or length of time elapsed since injury.
Khedr *et al.* [38]	1997	Prospective	55	Clinical examination and EDS	29%	Prevalence was attributed to 11% of patients having signs and symptoms of peripheral neuropathy and 18% with findings on EDS. CNP was associated with age >20 years, electric burns involving full-thickness skin and a %TBSA more than 20%.
Dauber *et al.* [37]	2002	Retrospective	358	Mailing patients questionnaires and inquiring if they had any pain	52%	Only 157 questionnaires completed, 23% survey response rate from the 1551 patients mailed questionnaires.
Schneider *et al.* [34]	2006	Retrospective	72	Clinical examination	40%	The most common associated sensation was a feeling of pins and needles in 46% of patients with pain.
Gabriel *et al.* [36]	2009	Prospective	370	Clinical examination and EDS	10.2%	Eight patients completed at least one follow-up examination. On follow-up examination there was significant improvement in clinical symptoms and EDS results without intervention. Four of the 8 patients were classified as having neuropathy with an evaluation at 71 days or less.
Brown *et al.* [7]	2011	Retrospective	492	Mailing patients questionnaires and inquiring if they had pain	18%	Study had a 23% response rate. Patients with CNP recalled significantly more procedures and dressing changes on questionnaires.
Tamam *et al.* [8]	2013	Retrospective	648	EDS	7.3%	Of the 47 patients with diagnosed peripheral neuropathy from EDS, 15 patients had polyneuropathy and 32 had mononeuropathy. Polyneuropathy was associated with a greater %TBSA, thermal burns, low-voltage electrical burns and upper and lower extremity burns.

%TBSA percent of total body surface area, *EDS* electro-diagnostic studies

Table 2. Comparisons between patients in the no-pain group and pain group following burn injury assessed by univariate analysis

	No-pain group (n = 1767)		Chronic pain group (n = 113)		
Comparison	n (%)	Median (IQR)	n (%)	Median (IQR)	*P*
Age, years	—	46 (31–59)	—	54 (39–62)	0.002
Sex					0.146
Male	1172 (66)	—	67 (59)	—	—
Female	595 (34)	—	46 (41)	—	—
Alcohol abuse	148 (8)	—	33 (29)	—	<0.001
Substance abuse	163 (9)	—	35 (31)	—	<0.001
Current daily smoker	585 (33)	—	83 (73)	—	<0.001
%TBSA	—	3.5 (2–8)	—	6 (3–25)	<0.001
Full-thickness burns	755 (43)	—	66 (58)	—	<0.001
Intubation/ventilation	239 (14)	—	37 (33)	—	<0.001
Number of burn surgeries	—	0 (0–1)	—	2 (1–6)	<0.001
Hospital LOS, days	—	3 (1–9)	—	11 (5–28)	<0.001

IQR interquartile range, *%TBSA* percent of total body surface area, *LOS* length of stay

Table 3. Odds of developing chronic neuropathic pain (CNP) following burn injury assessed by multivariate analysis

Comparison	OR	95% CI	*P*
Age, years	1.01	0.99–1.03	0.080
Alcohol abuse	2.04	1.06–3.94	0.030
Substance abuse	3.12	1.65–5.93	<0.001
Current daily smoker	6.91	3.72–12.67	<0.001
%TBSA	1.01	0.99–1.03	0.340
Full-thickness burns	1.83	0.46–1.96	0.510
Intubation/ventilation	1.91	0.98–3.73	0.060
Number of surgeries	7.51	2.91–19.21	<0.001
Hospital LOS, days	1.01	1.00–1.02	0.010

OR odds ratio, *CI* confidence interval, *%TBSA* percent of total body surface area, *LOS* length of stay

separate from neuropathic pain. Paresthesias were identified in 71.2% of their study population and neuropathic pain in 36.4% of the population [39]. Paresthesias may be painless prickling, burning, tingling, numbness and itching. However, these are symptoms of nerve injury and may cause significant distress for any patient with chronic involvement.

The limitations we identified through prior studies encouraged us to attain a large sample size, include all consecutive burn patients, provide multidisciplinary evaluations from different clinicians, use consistent definitions for nerve pain and chronicity and exclude patients with CNP attributed to an underlying illness or medication. The rigidity of our inclusion and exclusion criteria used to define CNP may explain the lower prevalence observed in our population.

Limitations of our study include the disproportionate comparative sizes of groups and retrospective study design. The sample size was small and the sample did not allow for a normal distribution, therefore we used the Fisher's exact test, Mann-Whitney *U* test, and reciprocal transformation to compare data between the no-pain and pain groups. Although we were able to compare different mechanisms of burn injury and complications, the small, unequal sizes of our samples limit the interpretation of data. With larger samples, we are less likely to encounter a type I error with statistical analysis. The retrospective nature of the study did not allow for patient interaction. We had to rely on detailed documentation from clinical notes, consistency between different provider notes and the appropriate amount of follow-up time to categorize our groups. Long-term follow-up care information was difficult to attain in international patients, homeless patients and patients with substance abuse or advanced psychiatric illness. We analysed data from a single adult burn center, limiting the generalizability of our findings in adult and pediatric populations. These findings may also vary when considering different anatomical locations. Although it is an American Burn Association-verified burn center, patient management differs from center to center, locally and internationally. Other burn centers may not incorporate the same level of multidisciplinary coordinated follow-up care for all admitted burn patients.

In the largest study to date, our findings suggest 6.01% of burn patients had an associated risk of developing CNP if they were older, abused alcohol, abused substances, were current daily smokers, had greater %TBSA burns, had full-thickness burns, were intubated on mechanical ventilation, had more surgeries and had a longer hospital LOS. Following multivariate analysis using reciprocal transformation for nonparametric data, substance abuse, current daily smoking, intubation on mechanical ventilation, number of surgeries and hospital LOS were all predictors associated with greater odds of developing CNP. Testing for multicollinearity with our stepwise regression model using forward selection determined our independent variables were indeed independent of each other, strengthening our findings. Current daily smoking and the number of surgeries performed were the two independent predictors with the greatest odds of developing CNP. The number of surgical procedures may be less of an association and more related to causality. Based upon these conclusions, burn patients with these associated predictors for developing

CNP may benefit from perioperative or early pharmacologic management and close follow-up [41–45]. Understanding the course of CNP can aid clinicians in prognosticating and managing burn patients.

Conclusion

The prevalence of CNP over 5 years was 6.01% in the burn center. Older age, alcohol abuse, substance abuse, current daily smoking, greater %TBSA burns, third-degree burns, being intubated on mechanical ventilation, having more surgeries and longer hospital LOS were all significantly associated with developing CNP following burn injury, when compared to patients who did not develop CNP following burn injury. Independent predictors for developing CNP were alcohol abuse, substance abuse, current daily smoking, having more surgeries and longer hospital LOS.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board (IRB00213320).

Consent for publication

Not applicable.

Availability of data and materials

The data used and/or analyzed during the current study are available upon request.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

The authors KMK, ALD and CSH all contributed equally to conception and design, acquisition of data, or analysis and interpretation of data. KMK drafted the manuscript. ALD and CSH revised it critically for important intellectual content. All authors KMK, ALD and CSH approved the final manuscript version to be published. All authors KMK, ALD and CSH agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of interest statement

None stated.

Abbreviations

CI: confidence interval; CNP: chronic neuropathic pain; EDS: electrodiagnostic studies; HO: heterotopic ossification; IRB: Review Board; ICU: intensive care unit; IQR: interquartile range; LOS: length of stay; OT: occupational therapist; QOL: quality of life; PT: physical therapist; OR: odds ratio; %TBSA: percent of total body surface area;

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