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Associations between traumatic stress symptoms, pain and bio-active components in burn wounds

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ABSTRACT

Objective: Pain and traumatic stress symptoms often co-occur. Evidence suggests that the neuropeptide oxytocine and pro-inflammatory cytokines are associated with both stress and pain. The aim of this pilot study was to explore relations between self-reported pain and traumatic stress, oxytocin and three cytokines in burn wounds.
Methods: An observational study in three burn centres was performed. Patients were invited to participate in the study when deep dermal injury was suspected. Patients completed the Impact of Event Scale (IES), a self-report questionnaire assessing traumatic stress symptoms, and they rated their pain the day prior to surgery. During surgery, eschar (i.e., burned tissue) was collected and stored at −80 ° C until analysis. When the data collection was complete, oxytocin and cytokine levels were analysed.
Results: Eschar from 53 patients was collected. Pain and stress scores were available from 42 and 36 patients respectively. Spearman correlational analyses showed an association between lower oxytocin levels at wound site and a higher total IES score (r = −0.37) and pain (r = −0.32). Mann-Whitney U tests comparing groups scoring high or low on pain or stress confirmed these associations.
Conclusion: These analyses lend support to a hormonal pathway that may explain how psychological distress affects pain at skin level in patients with traumatic stress symptoms.

1. Introduction

Pain is a problem following burns, often complicated by anxiety and acute traumatic stress symptoms (Giannoni-Pastor et al., 2016; Summer et al., 2007). Psychological theories such as the mutual maintenance theory (Sharp and Harvey, 2001) propose that physiological, cognitive, behavioral and affective factors of pain and posttraumatic stress influence and maintain each other. According to the Neuromatrix theory (Melzack and Katz, 2013), a leading pain theory, pain is a multidimensional experience in which sensory and psychological inputs play an important role. These theories suggest that pain and psychological distress share biological components. Underlying bio-active components such as cytokines and neuropeptides such as oxytocin (OT) are associated with both pain and psychological distress (Boll et al., 2017; van Zuiden et al., 2011). Furthermore, OT has been found to act on the fear response (Koch et al., 2014; Olff et al., 2013) which plays a role in posttraumatic stress symptoms. But few studies investigated these components in the skin despite the knowledge that the skin can act as a neuro-endocrine organ (Arck et al., 2006).

In response to a (burn) injury, cytokines are released trying to re-establish homeostasis (Melzack and Katz, 2013) followed by neurohormones, e.g., glucocorticoids and catecholamines, released through the hypothalamic-pituitary-adrenal (HPA) axis, and neuropeptides such as OT. OT is released either peripherally from the pituitary, central from paraventricular neurons or in the skin were it can be expressed by dermal fibroblasts and keratinocytes (Deing et al., 2013; Landgraf and Neumann, 2004; Rash et al., 2014). The presence of neuropeptides in the skin is assumed to result from both local synthesis, blood transport

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and release from nerve endings and immune cells (Slominski et al., 2015). As such it can bi-directionally communicate with the central system (Zmijewski and Slominski, 2011). There is ample evidence that OT plays a neuromodulatory role in (traumatic) stress and anxiety (Boll et al., 2017; de Kloet et al., 2005; Koch et al., 2014; Landgraf and Neumann, 2004; Neumann and Landgraf, 2012; Olff et al., 2013) and that emotional and environmental stressors can activate the skin stress response (Slominski et al., 2013).

Both OT and cytokines are related to pain. Most studies support analgesic effects of central administration of OT exerting a decreased sensitivity to noxious stimuli, be it that animal studies show more consistent findings compared to human studies (Boll et al., 2017; Rash et al., 2014). Recently, a study found evidence for analgesic effects after subcutaneous injection of OT (Gonzalez-Hernandez et al., 2017). Where OT seems to reduce pain, higher levels of pro-inflammatory cytokines were found associated with hyperalgesia: a study in rats receiving burns revealed that hyperalgesia was related to higher levels of the pro-inflammatory cytokine IL-6 in the skin (Summer et al., 2008). Another study has documented a role of inflammatory cytokines in the (neuropathic) pain process in which proinflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor α (TNFα) which are released by activated macrophages in wounds, showed to increase pain (Inoue, 2006).

Despite the plethora of studies on the associations between pain, stress, OT and pro-inflammatory cytokines there is a paucity of studies investigating its possible inter-relatedness in the skin. The aim of the current pilot study was to explore a relationship between self-reported pain and acute traumatic stress symptoms and bio-active components such as OT and pro-inflammatory cytokines measured in burned tissue (eschar) from patients with deep dermal or fullthickness burns. We hypothesize that these bio-active components are involved in a cross-talk interaction and that lower levels of OT and higher levels of cytokines in burn wounds are correlated with higher pain and traumatic stress scores.

2. Material and method

2.1. Participants

Participants were recruited at two Dutch and one Belgian burn centre between October 2011 and October 2012. Participants were included in the study if they were assumed to need skin grafting, were aged 18 years or older, and were Dutch or French-speaking. Individuals were excluded from the study if they had self-inflicted burns or a cognitive impairment that prevented reliable traumatic stress and pain estimates.

2.2. Procedure

The study featured a prospective design. Eligible patients were invited to participate into the study by a local researcher during the period of hospitalisation. All patients gave written informed consent after oral and written information about the study was provided. The researcher collected eschar during surgery and provided a questionnaire to the patient during the first week of admission to the hospital. Patients requiring mechanical ventilation were included in the study after they regained consciousness. Pain scores were assessed the day before surgery. The study was conducted according to the Helsinki Declaration and two institutional review boards in the Netherlands and Belgium boards approved the study.

2.3. Measures

Socio-demographics and burn characteristics such as age, gender, Total Body Surface Area (TBSA) burned, number of surgical procedures were recorded from the medical file. TBSA burned is the estimated percentage affected body area covered by partial and deep dermal injury.

The Impact of Event Scale (IES; Horowitz 1976) was used to assess acute traumatic stress symptoms related to the burn event. The Dutch validated scale was used in this study (Brom and Kleber, 1985). Fifteen items assess symptoms of intrusion and avoidance which are core symptoms of posttraumatic stress disorder, scored on a 4-point scale (0-1-3-5). Clinically significant symptoms were defined according to a cut-off of 26 (e.g., Bakker et al., 2013).

Overall pain in rest (background pain) was assessed using an 11-point graphic numerical rating scale ranging from 0 ‘no pain’ to 10 ‘the worst pain one can think of’ one or two days before surgery. All affected body areas were rated. A mean score was calculated if more than one pain score was provided.

Burn eschar was collected during surgery and stored at −80 °C until further use. Eschar is the unviable tissue resulting from deep dermal burned skin. It was transferred into cryovials which contained a stainless steel bead (Qiagen, Venlo, The Netherlands) and Lysis Buffer with Protease Inhibitor Cocktail (EMD Millipore, Billerica, USA). Biopsies were lysed using a TissueLyzer (Qiagen) for 5 min at 50 Hz. Aliquots of the supernatant were stored at −80 °C until further analysis was performed.

The magnetic bead panel Milliplex MAP kit (EMD Millipore, Billerica, USA) were used to analyse three cytokines (IL-1b, IL-6, TNF-alpha) and the neuropeptide oxytocin. The total amount of protein was determined using the colorimetric BCA total protein assay (PIERCE, Rockford, USA) according to the manufacturer instructions. Total protein levels were measured using the Nanodrop Spectrophotometer (Thermo Scientific, Wilmington, USA).

Neuropeptides were extracted from the tissues lysates using acetonitrile. 250 µl Tissue lysate was incubated with 375 µl acetonitrile for 10 min. After centrifugation, the supernatant was dried overnight using a Speed-Vac (Savant, Thermo Fisher Scientific, Breda, The Netherlands). Samples were then re-suspended in Assay buffer provided with the kit. Both cytokine samples and neuropeptide samples were aliquoted and either stored at −80 °C or used immediately for cytokine and neuropeptide analysis according to the manufacturer instructions (EMD Millipore).

The cytokine and neuropeptide levels were measured using Bio-Plex 200 (Bio-Rad, Hercules, USA) and data were analyzed using Bio-Plex manager software (Bio-Rad). The Milliplex MAP kits were measured using Bio-Plex 200 (Bio-Rad, Hercules, USA) and data were analyzed using Bio-Plex manager software (Bio-Rad). Cytokine and neuropeptide levels measured were divided by total protein levels of the samples and expressed as pg/mg protein.

2.4. Statistical analyses

Spearman correlations between pain, traumatic stress, cytokines and OT were calculated. Non-parametric tests, i.e., Mann-Whitney U tests, were used to investigate differences between groups of patients scoring low versus high on pain and traumatic stress. A cutoff point of 4 for pain and a cutoff point of 26 for clinically relevant stress levels were previously determined (de Jong et al., 2015) or commonly used (Bakker et al., 2013; Egberts et al., 2017) to indicate low pain and stress scores. Analyses were performed using SPSS 24.

3. Results

3.1. Participants

Sixty patients provided written informed consent. Eschar from 52 participants was collected. Of these, 10, 19 and 23 participants respectively were admitted to the burn centres in Beverwijk, Brussels and Rotterdam. Participants were predominantly male (n = 34; 65%), they were on average 47 years old (SD = 18). Burn severity in terms of total

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