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Effective symptomatic treatment for severe and intractable pruritus associated with severe burn-induced hypertrophic scars: A prospective, multicenter, controlled trial[☆]

Jun Wu^{a,1,*}, Rui Xu^{a,1}, Rixing Zhan^{a,1}, Gaoxing Luo^{a,1}, Xihua Niu^{b,1}, Yi Liu^{c,1}, Benjamin Tak-Kwong Lee^{d,e}, Meinrad Flury^e, Chun-Ho Wong^{d,e}, Manson Fok^{d,f}, Johnson Yiu-Nam Lau^{a,d,g}

^aInstitute of Burn Research, State Key Laboratory of Trauma, Burns and Combined Injuries, Chongqing Key Laboratory for Disease Proteomics, Southwest Hospital, Third Military Medical University, Chongqing 400038, China

^bDepartment of Burn, Zhengzhou First People's Hospital, Zhengzhou 450000, China

^cLanzhou General Hospital, Lanzhou Command of China People's Liberation Army, Lanzhou, Gansu 730050, China

^dMJ Medical Gel Systems Ltd., No. 6 Science Park West Avenue, Hong Kong Science Park, Shatin, Hong Kong SAR, China

^ePolyGum Technologies Ltd., Hong Kong Science Park, Shatin, Hong Kong SAR, China

^fFaculty of Health Sciences, Macau University of Science and Technology, Avenida Wai Long, Cotai, Macau SAR, China

^gDepartment of Applied Biology and Chemical Technology, Hong Kong Polytechnic University, Hung Hom, Hong Kong SAR, China

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ABSTRACT

Background: Burn-induced hypertrophic scars are disfiguring and can be associated with severe and intractable pruritus. No effective treatment modalities are currently available for symptomatic control of pruritus for most patients. We assessed the effect of the Antipruritic Hydrogel (CQ-01) in the symptomatic treatment of severe and intractable pruritus associated with burn-induced hypertrophic scars in a prospective, multicenter, controlled trial.

Methods: A pilot study was conducted in healthy adult volunteers to identify the most appropriate hydrogel formulation. A selected preparation called Chongqing No. 1 (CQ-01; a guar gum-based hydrogel impregnated with peppermint oil, menthol, and methyl salicylate by a nanoemulsion), showed an excellent symptomatic relief in an exploratory study in 2 patients with intractable pruritus. A statistically powered, prospective, multicenter, controlled study was then conducted in 74 patients to evaluate the efficacy and safety of a 24-h application of CQ-01 compared to a gel control and a negative control on three separate areas in each patient. Symptom assessment was based on our visual analog JW scale (ranging from 0 to 100) at baseline and various time points up to 7 days after application. Follow-up studies were conducted to determine the reproducibility of CQ-01 in repeated applications.

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* Corresponding author. Tel.: +86 139 8313 0289; fax: +86 23 6546 1677.

E-mail address: jun.wu@burnstrauma.com (J. Wu).

¹ Equally contributing authors.

Abbreviations: JW scale, Jun Wu scale; CQ-01, Chongqing No. 1; CQ-02, Chongqing No. 2; WVTR, water vapor transmission rate; VAS, visual analog scale; ITT, intention-to-treat; PP, per protocol.

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Results: Of the 74 enrolled subjects, the only observed adverse event was skin irritation reported in 6 patients (8%) and resolved shortly after gel removal. Compared to the baseline, the gauze negative control had a mean JW score reduction of 7; while the gel control and CQ-01 had a drop of 18 ($p < 0.001$) and 36 ($p < 0.001$), respectively. The CQ-01 clinical effect was significant for up to 3 days and waned slowly from 3 to 7 days. There was no statistical correlation between the treatment response and any of the demographic, patient or burn-related factors. Further studies showed a trend that repeated applications might be more effective, suggesting the absence of tachyphylaxis.

Conclusions: This prospective, multicenter, controlled study showed that this novel hydrogel CQ-01 is safe and provides significant symptomatic relief for severe and intractable pruritus associated with hypertrophic scars, an unmet medical need for these patients. This effect is independent of the etiology of the burn trauma, extent of the scarring, and duration of the scar formation.

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1. Introduction

When normal skin is damaged the body repairs itself with potential scar formation [1–3]. In patients with genetic predisposition [4] and deep thickness skin loss, hypertrophic scars may result [5,6]. For hypertrophic scars, the major clinical issue is pruritus [7], and in severe cases, can cause sleep disturbance/deprivation [8], poor quality of life [9], depression [10], and in extreme cases, suicidal tendency [11]. There is currently no effective treatment [12,13].

Burn-related injury is a major global health issue (265,000 deaths per year estimated by the World Health Organization, 2014). In China, there is an estimated 15–20 million burn cases annually (incidence rate 1.0–1.5%) with 2–3 million undergoing hospitalization (Burn Institute Estimation, 2014). Being the largest Burn Center in China, we challenged ourselves to address this unmet medical need. Literature and our experiences indicated that a partial symptomatic relief can be achieved when the scar area is exposed to a cool surface or environment [14] while high ambient temperatures or dryness exacerbates pruritus. Firm touching or massaging also alleviated pruritus [15,16], but silicone sheets were ineffective [17]. A report claimed that 2% topical salicylic acid-containing hydrogel provided some symptomatic relief in 3 patients [18]. Steroid and anti-histamine-based creams were largely ineffective [19].

Based on the information, we identified a guar gum-based hydrogel (CQ-01) from a number of medical gel prototypes that coupled with nanotechnology for optimal cooling effect and minimal irritation. Here, we report a statistically powered, prospective, multicenter, controlled study that evaluated the safety and efficacy of CQ-01 in the relief of severe to intractable pruritus in burn patients.

2. Materials and methods

2.1. Development of the Antipruritic Hydrogel “CQ-01”

The proprietary guar gum-based hydrogel [20,21] has a high water content with excellent safety profile. The high flexibility

provided maximum contact as an occlusive patch for uneven scar contours. The hydrogel was non-sticky to skin and possesses high water vapor transmission rate (WVTR), as a measure of breathability, measured by a modified ASTM E-96 method [22].

Several prototypes were prepared with different concentrations of peppermint oil (0–3.6%), menthol (0–2.5%), and methyl salicylate (0–11%). As the oily consistency of organic additives exacerbate pruritus, a proprietary oil-in-water nanoemulsion [23] was used to formulate a non-oily hydrogel and deliver these additives in a controlled release fashion.

2.2. Clinical studies

Three different formulations were tested in 8 healthy volunteers based on 3 clinical parameters (cooling sensation, warming sensation, and erythema on the applied areas). The selected prototype (CQ-01) was tested in an exploratory study in two patients with intractable pruritus from burn-induced hypertrophic scars.

A prospective, multicenter, controlled study was then designed to evaluate the efficacy and safety of CQ-01. Three major burn centers participated were (a) the Institute of Burn Research, Southwest Hospital, Third Military Medical University, (b) Zhengzhou First People's Hospital, and (c) Lanzhou General Hospital with 220, 170, and 50 beds for burn patients, respectively.

The symptoms were assessed using the JW scale (Table 1), which is a standard pruritus severity VAS scale for monitoring symptomatic changes [24] and is adopted by the Burn Institute of Southwest Hospital in Chongqing, China. This scale also integrates pruritus intensity and quality of life in terms of depression and sleep quality for assessing the burn patients in a comprehensive manner [25]. In our experience, there is a good correlation between the symptom descriptors and pattern of sleep disturbance. In this study, only the symptom descriptor will be used. Patients were taught of the JW scale at the baseline and all subsequent time points were assessed based on a visual analog scale (VAS) version of the JW scale.

To ensure statistical power, the following assumptions/criteria were adopted: clinical JW score improvement of ≥ 20 ,

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