Ultrasonics xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Ultrasonics

journal homepage: www.elsevier.com/locate/ultras

Using therapeutic ultrasound to promote irritated skin recovery after surfactant-induced barrier disruption

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ARTICLE INFO

Keywords:
SLS
Skin barrier disruption
Water content
Therapeutic ultrasound

ABSTRACT

Background: Surfactant-induced skin barrier disruption can enhance blood flow and water content in the superficial skin. The effect of therapeutic ultrasound on accelerating the recovery of superficial skin after skin barrier disruption has seldom been studied.

Objective: To understand the effects of therapeutic ultrasound on barrier recovery, we used the sodium lauryl sulfate irritation model and treatment with ultrasound intervention.

Methods: The study allocated 30 healthy subjects into an ultrasound group (n = 15) and a control group (n = 15), each divided into three subgroups (sodium lauryl sulfate at concentrations of 1.0%, 0.5%, and 0%). Pulsed ultrasound (1 MHz, 0.3 W/cm^2_{SATA}) was applied to ultrasound subgroups. The treatment effect was evaluated by the recovery rate of enhanced blood flow and water content.

Results: The results indicated a surfactant dose-dependent effect on blood flow, but not on water content. The recovery rates of enhanced blood flow were higher in the 0.5% and 1.0% ultrasound subgroups than in the control subgroups throughout the experiment. However, recovery rates of water content were higher in the ultrasound subgroups than in the control subgroups only on Day2.

Conclusions: Pulsed ultrasound accelerated the barrier recovery by reducing the enhanced blood flow and water content after skin barrier disruption.

1. Introduction

Ultrasound (US) is used widely in medicine as therapeutic tool for soft tissue lesions. Through both thermal and nonthermal mechanisms, US can promote healing in a variety of soft tissues, such as tendons, ligaments, joint capsules, and fascia [1,2].

Several studies have demonstrated that pulsed US promotes cutaneous tissue repair of diabetic wounds, skin flaps, and incisional wounds [3–7]. To sum up the aforementioned research regarding the early intervention on acute damage to skin tissue, US (pulsed, 0.75–3.0 MHz, 0.1–0.5 W/cm^2_{SATA}) can increase the collagen deposition and tissue tension of wounds, thus improving the survival rate of the skin flaps, as well as the blood vessel formation, epidermal cell proliferation, and vessel formation rates [3–7]. While the above interventions covered all the layers of cutaneous tissue, they did not focus on therapeutic US for superficial skin damage to the dermis and epidermis.

A dysfunctional barrier can be observed in various skin diseases, such as atopic dermatitis. When the skin barrier is disrupted, the disruption can simultaneously cause epidermal DNA synthesis and increase the release of cytokines [8,9], which facilitate the process of tissue repair. Choi et al. have demonstrated that the TGF-β of normal dermis and epidermis is upregulated after US treatment [10], suggesting that US intervention may accelerate activation in the inflammatory phase and promote the next proliferative stage of tissue [11]. Moreover, Mortimer & Dyson have reported that US can change the calcium permeability of the cell membrane in fibroblasts [12]. The increased concentration of intracellular calcium ions can activate the appropriate calcium-sensitive signal transduction pathways in the cell, thus promoting fibroblast proliferation [12]. Although no direct evidence suggests that the clinical advantages of ultrasound are due to altered membrane permeability and cytokines [13], Dyson has suggested that these changes could account for the promoted tissue repair

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https://doi.org/10.1016/j.ultras.2018.08.007
Received 20 November 2017; Received in revised form 10 July 2018; Accepted 12 August 2018

after treatment with ultrasound [11].

Artificial disruption of the skin barrier is a type of damage to the skin barrier caused by a surfactant, an organic solvent [14]. According to the standard guidance published by the European Society of Contact Dermatitis (ESCD), sodium lauryl sulfate (SLS) is an anionic surfactant used extensively as a surfactant for skin barrier disruption [14]. It has been applied in dermatological research as a model of barrier disruption [15,16]. The surfactant destroys the lipids of the stratum corneum and thereby disrupts the barrier function of the skin, after which it permeates through the epidermal and dermal layers to cause a slight irritant reaction. In human stratum corneum cells, SLS increases the expression of cytokines, which leads to endothelial dysfunction and is characterized by vasodilation and increased capillary permeability [17,18]. The resulting syndrome from SLS irritation is clinically associated with increased blood flow and water content in human dermis [18,19]. Some in vivo studies have also found that the cytokine and skin blood flow in human forearm skin increased according to the SLS dosage, indicating an SLS dose-dependent effect on barrier damage [16,18,20]. Although it has been suggested that the irritation by topical administration of SLS can be used in clinical and experimental research [14,15,21], no previous studies have examined the application of US for barrier disruption in the irritation model.

To understand the effects of therapeutic US on barrier recovery, US was applied to the skin under the SLS-irritation model. This study aimed to test the hypothesis that US can promote barrier recovery by reducing the enhanced blood flow and water content after skin disruption. In this study, the model was used for studying the effect of US on the changes in superficial dermis, wherein one forearm of each participant in both groups was selected to receive SLS stimulation. Therapeutic US (1 MHz) was used as a stimulation method to deliver the sound waves to the irritated skin, and the skin blood flow and water content were quantitatively assessed by laser Doppler flowmeter and dielectric constant analyzer. Details of the current study are presented as follows.

2. Methods

2.1. Participants

The experimental protocol was approved by the institutional review board of Chung Shan Medical University Hospital, and informed consent for the study was obtained from all human subjects in accordance with the WORLD Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects; Trial Registration: ClinicalTrials.gov (NCT02257281). In total, 30 participants were recruited for this study with a poster approved by the Institutional Review Board. The 30 healthy subjects were randomly divided into two groups: an US group and a control group. All subjects were examined by doctors, and unsuitable subjects were excluded from the study. After the investigator explained the content to the subjects and they completely understood the test, they signed the informed consent. Healthy volunteers, males and females aged 20 to 45, were admitted. The exclusion criteria included vulnerable groups, metabolic disorders, malignancy, autoimmune diseases, allergies, irritant contact dermatitis, inflamed or infected skin, and persons meeting US treatment contraindications. The contraindications for US include infection, neoplasms, cancer, growing epiphyseal plate, metal pins, lack of sensation, and venous thrombosis [22]. Additional exclusion criteria included smoking or drinking, a recent blood extraction from the arm, aerobic exercise, medication (such as corticosteroid or adrenocorticotropic hormones), and excessive exposure to the sun near the experimental period.

2.2. Skin barrier disruption

Three circles of 2 cm in diameter were labeled along the midline of the volar forearm at 5, 10, and 15 cm distal to the antecubital crease. SLS (purity ≥ 99%, Sigma-Aldrich, Sigma Chemicals Co., St. Louis, MO, USA) and sterile water were mixed to prepare SLS solutions of three concentrations: 1%, 0.5%, and 0%. A pipette was used to drip the 60 µl SLS solution into 12 mm Finn chambers with paper filter discs (Epitest Ltd, Oy, Finland). The centers of the circular blocks were covered with Finn chambers with 1%, 0%, and 0.5% SLS solution, respectively, from the proximal to distal circles. Afterwards, the Finn chambers were affixed with non-occlusive dressing to the volar forearm and left for 24 h before removal. On removal of the SLS patches, the skin was gently washed with saline solution and allowed to dry. The day the chamber was removed was defined as Day0. The day following Day0 was defined as Day1, when the skin presented circular erythema (Fig. 1) [19]. Thus, disruption of the artificial skin barrier was completed. The homeostatic repair response began after skin barrier disruption [23]. Gradually, the barrier disruption in the dermal layer would recover [19,24].

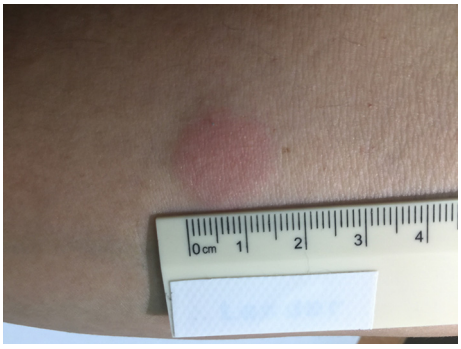

Fig. 1. Marked erythema induced by application of SLS. The erythema (1.0% SLS) was irritated on Day1.

2.3. Application of ultrasound

After the skin barrier disruption was completed, US intervention was applied twice daily to each erythema of the US group at fixed times (9:00 a.m. and 4:00p.m.) from Day1 to Day4, while the erythemas of the control group were free of US intervention. The US application was applied by a licensed physiotherapist. Each erythema was treated with 1.5 W/cm^2 (spatial average temporal peak, 20% duty cycle, 1 MHz) for 10 min. The machine model was a Sonopuls 692 with a 1.0-cm transducer head having a 0.5 cm^2 effective radiating area (Enraf Nonius BV, Rotterdam, the Netherlands). The operator moved the transducer head smoothly in circular motions. To ensure that the treatment was equal for all subjects, the probe was applied within the circular block. The jelly used for transmission was OptiLube Lubricating Jelly (Optimum Medical Solutions, UK). Additionally, the transducer head was sterilized by 75% alcohol before each US intervention.

2.4. Skin blood flow

Skin blood flow is one of the most important biophysical parameters for evaluating human skin barrier disruption [16,25,26]. To evaluate the increased blood flow caused by the skin irritation, a laser Doppler flowmeter (MoorVMS-LDF1; Moor Instruments Ltd., Devon, UK) was used according to the guidelines of the ESCD Standardization Group [25]. Doppler flowmetry is a noninvasive technique that measures the velocity of moving erythrocytes to a depth of approximately 1 mm. After the subject rested supine for about 15 min, the flow probe was applied with an adhesive holder to the center of the circular block, which had been drawn previously. The data during a period of 5 min were averaged for analysis. The measured data of normal skin before skin barrier disruption were defined as the baseline. The measurements were completed before nine o'clock in the morning from Day1 to Day5.

SLS-irritated barrier disruption is clinically associated with