Aloe vera gel phonophoresis versus silver nanoparticles phonophoresis on burn wound: a prospective randomized double-blinded trial
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Introduction
Burn is an injury to the skin or other organic tissue primarily caused by heat, radiation, electricity, friction, or contact with chemicals. The severity of burn injuries depends on the depth of the wound injury and the extent of the body area affected [1]. Healing burn wounds depends on many factors, which include the degree of burn (type I–IV), quality and cause (for instance, chemical or thermal), and the general condition of the patient [2]. Numerous mechanisms, together with coagulation, inflammation, matrix synthesis and deposition, angiogenesis, fibroplasia, epithelialization, contraction, and remodeling occur during the healing of burn injuries [3]. Growth factors control cellular migration, attachment, proliferation, differentiation, maturation and matrix synthesis, and exert a powerful influence on the process of wound repair [4].

Aloe vera has been utilized in the conventional medicine for a long time. It incorporates many crucial nutrients for the body, which include amino acids, B vitamins, and other nutrients that support general health. It has pharmacological properties including antioxidant, wound healing, antibacterial, antifungal, and immunomodulation effects [5]. Aloe vera suggests a beneficial effect on wound healing by reducing the inflammation [6]. It increases the activity of macrophages, monocytes, and stimulation of killer T lymphocytes. Aloe vera gel also can block the formation of prostaglandin and thromboxane from arachidonic acid to reduce inflammation within the wound [7]. It can also have an inhibitory effect on the pathogenic microorganism that inflict meal poisoning or distinctive illnesses in human beings [8].

Nanoparticles may be described as 'solid particles with a size in the range of 10–1000 nanometer (nm).' Silver nanoparticles (SNPs) usually present at 1–100 nm in

Background
Burn trauma ranges from a minor burn to devastating injuries, which can affect all aspects of a person’s life including esthetic appearance, relationships with others, and psychological, social, and physical functioning.

Objective
This study was conducted to compare the effect of aloe vera gel phonophoresis and silver nanoparticles (SNPs) phonophoresis for second-degree burn wound healing.

Patients and methods
Forty patients with second-degree burn wounds were included, and their age ranged from 20 to 40 years. Patients were randomly assigned into two groups: group A underwent aloe vera gel phonophoresis and group B underwent SNPs phonophoresis. All treatment interventions were applied at a frequency of three sessions per week for 12 weeks. Outcome measures were performed through wound surface area in cm² via Transparency Method, which is the tracing method. The assessment was done before treatment, after 6 weeks, and after 12 weeks of the treatment.

Results
There was a highly significant decrease in the wound surface area between aloe vera gel phonophoresis (group A) compared with that of SNPs phonophoresis (group B) (P<0.0001).

Conclusion
It was concluded that aloe vera gel phonophoresis has greater efficacy than SNPs phonophoresis for treating second-degree burns.

Keywords:
aloe vera gel, burn, phonophoresis, silver nanoparticles, wound healing

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size in at least one dimension [9]. As particle size decreases, the surface area-to-volume ratio of SNPs increases dramatically, which leads to significant modifications in their physical, chemical, and biological properties. SNPs have a significance interest in biomedical applications, because of their antibacterial, anti-fungal, antiviral, anti-inflammatory effects and wound healing improvement, which could be exploited in developing better dressings for wounds and burns [10]. SNPs interact with proteins and enzymes of thiol groups [11] and disrupt processes including cell respiration, ion transport across membranes [12], ATP production, and DNA replication capability [13] and decrease the activity of microorganisms.

Phonophoresis is the process of increasing skin absorption and penetration of the topical medications to the deep tissues using ultrasound. The implementation of the therapeutic drugs relies on different factors such as rate, amount, drug penetration depth of the skin, and the potential drug toxicological hazards on the tissues. Local anesthetics, counterirritants, and anti-inflammatory drugs are used in phonophoresis. Phonophoresis is a noninvasive, painless approach that has fewer adverse effects, is well tolerated, and has been utilized in musculoskeletal and dermatologic disorders [14]. The purpose of the present study was to compare the efficacy of aloe vera gel versus SNPs phonophoresis on the burn wound.

**Patients and methods**

A prospective, randomized double-blinded trial was conducted between January 2017 and October 2017. Patients were recruited from volunteered patients who had been admitted to Kaser El-Aini Hospital, Cairo. This study was done in 40 patients (22 male and 18 female) with second-degree burn wound. Patients’ total body surface area was 15–35%, and their age groups ranged from 20 to 40 years; they were free of any other illness that might affect the results. Patients having life-threatening disorders such as renal failure, myocardial infarction, diabetes, peripheral vascular diseases, hyperthyroidism, acute viral diseases, and electrical and chemical burns were excluded. The protocol of this study was authorized by the ethical committees for scientific research of the Faculty of Physical Therapy, Cairo University, Egypt. All patients were given a full explanation of the treatment protocol, and signed informed consents were obtained for participation and publication of results.

The sample size was calculated by using G power (Heinrich-Heine University of Dusseldorf, Kiel, Germany) program; a preliminary power analysis [power (1α error $P$)=0.85, $α=0.01$, effect size=0.5] determined a sample size of 20 patients per group would be required for statistical analysis. This effect size was chosen because it yielded a realistic sample size [15].

**Unrestricted (simple) randomization**

Unrestricted randomization was done as follows: combine the 20 sealed group A envelopes with the 20 sealed group B envelopes and shuffle as you would a deck of cards. Once you are satisfied that the deck of envelopes is shuffled very thoroughly, with a firm hand, mark a unique number on the front of each envelope sequentially from 1 to 40, with a pen. The carbon paper inside the envelope will transfer this number to the allocation paper inside. Place these envelopes into the plastic container, in numerical order, ready for use [16].

The patients were randomly assigned to the group A (20 patients, with 9 female and 11 male) or the group B (20 patients, with 8 female and 12 male) by another independent therapist who took a sealed opaque envelope from a box following a numerical sequence; the envelope contained a letter indicating whether the patient would be allocated to the aloe vera gel phonophoresis (group A) or SNPs phonophoresis (group B). Both groups were compared regarding patient demographics including age and sex.

**Instrumentation**

The following instrument was used.

**Ultrasound unit**

Sonopulse 590 Ultrasound Device: Nonius, sonopuls 590, S.NO.03-202 type 14663.900 is a therapeutic ultrasound device manufactured by Enraf Holland (Birmingham, West Midlands, United Kingdom), and it was used to conduct this study with the following parameters: pulsed mode at 100 Hz, duty cycle of 10%, frequency of 1 MHz, intensity of 0.5 W/cm² and an effective irradiation area of 1.0 cm². Ultrasound was applied for 5 min, using the method of a direct coupling and oscillatory rubbing movements.

**Procedure**

The assessment procedures

Transparency method: in this study, two sterilized sheets of transparency (polyester film sheet, A4 size, 210 mm×297 mm, 100 μm in thickness) were directly placed over the wound and the perimeter of the wound was traced by using a permanent marker pen. The orientation of the wound and the position of the patient at the time of tracing were recorded. Care was taken to avoid movement of transparency and
exertion of pressure over the wound to avoid distortion. The upper sheet was used for surface area measurement and the lower sheet, which was in contact with the wound, was disposed of. Transparency with an outline of the wound by the permanent marker pen was taken for wound surface area measurement by use of a computer software; the surface area was calculated in cm² by tracing the outline of the wound edge [17].

The captured digital images were transferred in the transfer image file format to retain maximum image quality with a frame grabber in the computer, using the AutoCAD 2004 software (Autodesk, Inc., Mill Valley, California, United States of America), which is used for measurement of surface area. The actual procedure was after feeding the image to a computer in AutoCAD 2004 software; the wound margins were delineated by mouse, and then the surface area of the wound was calculated by the software automatically. The computer software was used to finally calculate the surface area applying its command [17]. The assessment was done before treatment, after 6 weeks (post I) and after 12 weeks (post II) of the treatment.

Treatment procedure

**Group A: aloe vera gel phonophoresis**
The patient sat in a comfortable position. The burn wound had been cleaned with saline and then aloe vera gel was applied to the skin. The sterilized glove packed with ultrasound gel was put on the wound and then the ultrasound was implemented by the therapist. The ultrasound parameters were set as follows: frequency: 1 MHz, intensity: 0.5 W/cm² and the treatment time was 5 min. Finally, the wound was cleaned, and the sterile dressing had been connected to wound. We applied three sessions per week for 12 weeks.

**Group B: silver nanoparticles phonophoresis**
The patient sat in a comfortable position. The burn wound had been cleaned with saline, and then SNPs were applied to the skin. The sterilized glove that had been packed with ultrasound gel was put on the wound, and then the ultrasound was implemented by the therapist. The ultrasound parameters were set as follows: frequency: 1 MHz, intensity: 0.5 W/cm² and the treatment time was 5 min. Finally, the wound was cleaned, and the sterile dressing had been connected to the wound. We applied three sessions per week for 12 weeks.

Statistical analysis
All statistical analysis was conducted through the statistical package for the social studies (SPSS, version 19) for Windows (IBM SPSS, Chicago, Illinois, USA) [18]. *t* Test was conducted for comparison of the mean age between both groups and $\chi^2$ was conducted for comparison of sex distribution between groups. Multivariate analysis of variance with repeated measures was conducted to compare the mean values of wound area between before, post I, and post II measurements in each group. Post-hoc tests using the Bonferroni’s correction were carried out for subsequent multiple comparisons. *t* Test was conducted for comparison between groups at the three times of measurements. The level of significance for all statistical tests was set at $P$ value less than 0.05.

Results
A diagram of the patients’ randomization in the study is shown in Fig. 1. A total of 55 patients were initially screened. After the screening process, 40 patients were found to be eligible to participate in the study. In total, 40 (100%) participants completed the treatment program.

Demographic characteristics of the patients in both groups A and B
Table 1 showed the mean±SD age of groups A and B. There was no significant difference between both groups in the mean age ($P=0.65$). Moreover, there was no significant difference in sex distribution between groups ($P=0.74$).

Effect of treatment on wound surface area

**Within-group comparison**
Both groups showed similar results in a comparison between the three-time intervals. There was a significant decrease in wound surface area at post II compared with that at the post I and before treatment ($P>0.001$). Moreover, there was a significant decrease wound surface area at the post I compared with that at before treatment ($P>0.001$) (Table 2 and Fig. 2).

**Between groups’ comparison**
There was no significant difference between both groups in wound surface area before treatment ($P=0.898$). Comparison between groups A and B after treatment revealed a nonsignificant difference in wound surface area at the post I ($P=0.16$), whereas there was a significant decrease in wound surface area of group A compared with that of group B at post II ($P=0.01$) (Table 2 and Fig. 2).

Discussion
The present study was designed to compare the efficacy of aloe vera gel phonophoresis (group A) as opposed to SNPs gel phonophoresis (group B) intervention in
improving burn wound healing. Results of this study revealed that there was no significant difference between both groups in wound surface area before treatment ($P=0.898$), and comparison between groups A and B after treatment revealed a nonsignificant difference in wound surface area at post I ($P=0.16$), whereas there was a significant decrease in wound surface area of group A compared with that of group B at post II ($P=0.01$) (Table 2 and Fig. 2).

This could prove that aloe vera gel phonophoresis (group A) shows better improvement than SNPs gel
phonophoresis (group B), and this comes in agreement with Oryan et al. [19], who found that the aloe vera gel accelerates the rate of wound contraction, epithelialization, and then maturation. Vázquez et al. [20] achieved that at the earlier stages of tissue healing, there is reduced overall cellularity edema and fibrin clot together with macrophages and fibroblasts discovered in the dealt with lesions, that is, those treated with aloe vera, in contrast to the controls, which recommends that aloe vera enhances the rate of the inflammatory phase of tissue healing.

Introduction of sufficient blood flow within the injured area increased the number of endothelial cells, macrophages and fibroblasts, in addition to the superior maturation of the fibroblasts, which lead to accelerated collagen manufacturing by means of these cells.

Liu et al. [21] investigated how the SNPs had an effect on particular cells during the wound recovery process. The cellular reaction of keratinocytes and fibroblasts, from an excisional wound version in rodents, had been studied in this text. The rate of wound contraction was decided by means of standardizing the wound site area upon a time. Liu et al. [21] stated that the SNPs enhanced re-epithelialization by means of improved keratinocyte migration and proliferation, and wound contraction, by using the schism on fibroblasts in myofibroblasts. These mechanistic explanations concerning the SNPs’ enhancing wound care performance, by way of shortening the recovery period of the wound.

In addition, the results of this study were supported by AshaRani et al. [22] who examined the harmfulness of SNPs on the genome of human cells to reason that SNPs enter the cell and the nucleus and to the hereditary material and SNPs capture the cell cycle in the G2 period of mitosis, which can make harm cells. So it is compatible with the absence of epithelialization in the SNPs (group B) is because of this action. This implies the harmful effects of SNPs on the multiplication of epithelial cells in mitosis, which prompts delayed tissue healing. The toxicity effects of SNPs on the proliferation of epithelial cells in mitosis lead to delayed recovery. When comparing between aloe vera and SNPs post-treatment effects, it revealed a nonsignificant difference in wound surface area at post I ($P=0.16$), whereas there was a significant decrease in wound surface area of aloe vera compared with that of SNPs at post II ($P=0.01$).

Chen and Schluesener [11] in an examination of the dangers of SNPs inferred that SNPs thought process a sharp lower in the mitochondrial diversion and prompt cell malfunction. It had been discovered that silver ions appear to disorganize mitochondria via interactions with thiol agencies of the mitochondrial inner membrane. As these consequences of silver ions can be completely obstructed through sulfhydryl reagents (e.g. decreased glutathione), the findings absolutely recommended that mitochondria had been underneath oxidative stress while the cells were exposed to silver ions [11].

The end result of this research shows that the aloe vera gel phonophoresis accelerates wound recovery, as has been investigated in several studies [19,20].

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<th>Table 2 Mean wound surface area before treatment and post I and post II in groups A and B</th>
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MANOVA, multivariate analysis of variance; MD, mean difference. *Nonsignificant. **Significant.

Figure 2

Mean values of burn wound area (cm²) of Aloe vera gel and silver nanoparticles phonophoresis groups’ before treatment and post I and post II.
studies, excellent outcomes have been taken from the SNPs phonophoresis in conjunction with different substances [21]. However, this observation indicates that SNPs phonophoresis partially reduce the rate of wound healing [11,22]. The current study has some limitations: the small sample size and short duration of the treatment period. More extensive studies assigning the efficacy of aloe vera gel versus nanosilver gel phonophoresis on deep partial thickness burn wound are needed. Further studies should be undertaken to use the large sample. Further studies should be carried on patients with another wound like an ulcer. Further investigations are needed to compare between different frequencies and different intensities of ultrasound to detect the most beneficial frequency and intensity that can be used for drug delivery for improving burn wound healing. Similar studies should be conducted using other nanoparticles.

Conclusion
It could be concluded that aloe vera gel phonophoresis is more effective than SNPs phonophoresis in decreasing the wound surface area and in accelerating the burn wound healing.

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Nil.

Conflicts of interest
There are no conflicts of interest.

References