Comparison of the effectiveness of Aloe Vera Gel with 2% Nitrofurazone ointment on the healing of superficial second-degree burns. Randomised clinical trial

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Abstract
Background Burn injuries are one of the most common sources of trauma globally that comprise a significant drain on long-term personal and healthcare cost. Large surface area burn wounds are difficult to manage and may result in significant physiologic and psychological sequelae. The aim of this study was to compare the effectiveness of Aloe Vera gel with Nitrofurazone ointment in the healing of superficial second-degree burn wounds.

Methods The present study was a split body controlled, randomized clinical trial. The sample was recruited from patients with superficial second-degree burn wound who were prescribed to treat with 2% Nitrofurazone ointment. Thirty patients with at least two burn, each burn on an alternate side of the body, entered the study — samples allocated to two groups which received Aloe Vera gel or 2% Nitrofurazone ointment on their burns. Bates-Jensen Wound assessment tool (BWAT) was used to evaluate the healing of burns. The burns were evaluated before, one, two and three weeks after the beginning of treatment.

Results The mean ± SD of BWAT scores in Aloe Vera zones were 30.32 ± 3.28, 27.33 ± 3.38, 21.33 ± 3.13, 16.12 ± 2.16 respectively (F(2, 65.07) = 440.00, p=0.001). The mean ± SD of BWAT scores in Nitrofurazone ointment zones were 30.51 ± 3.79, 28.45 ± 3.49, 23.36 ± 2.89, 19.23 ± 2.11 (F(1, 52.00) = 228.00, p=0.001).

Conclusions There is a significant difference in (BWAT) scores between intervention and control groups. Aloe Vera gel was as effective as Nitrofurazone ointment in the treatment of superficial second-degree burns.

Trial registration IRCT2014113020151N1. Registered 14 December 2014, https://www.irct.ir/trial/17874

Background
Burn injuries are among the most common causes of hospitalization (1, 2). They are responsible for 5% of hospitalization worldwide and have a higher burden in developing countries (3). About 90% of burns occur in Low and middle-income countries, where health facilities are more limited (4). Patients with burn injuries are at risk of short and long term complications (5). Delay in burn wound healing is
one of these complications (6). The healing of burn wounds is very critical in the process of recovery and rehabilitation of these patients.

Burns can occur when the skin is exposed to a high degree of heat from fire or hot liquids, electricity, chemicals, or radiation. Burns are classified according to the severity of tissue damage. First-degree burns affect only epidermis and cause pain and redness. Second-degree burns extend to the dermis causing pain, redness, and blisters that may discharge. Third-degree burns include both layers of the skin and may also damage the underlying tissues including bones, muscles, and tendons. The burn site appears pale, charred, or leathery. There is no pain in the burned area because the nerve endings are destroyed. Fourth-degree burns extend through the skin and subcutaneous tissue into the underlying muscle and bone (7).

Second-degree burns involve the epidermis and part of the dermis. They are divided into superficial and deep. These burns are very painful and the risk of infection, scarring development and delay in healing is high in them (8). Deep second-degree burns may progress to third-degree burns in several days. Dressing burns with medicines that help wound healing can have an important role in reducing complications. All burns may cause complications if not properly treated (9).

One of the routine treatments of superficial second-degree burns is daily washing and dressing with Nitrofurazone (2%) ointment (10). Nitrofurazone is a topical anti-infective agent which is effective against gram-negative and gram-positive bacteria (11). This ointment is widely used to treat various types of superficial wounds including burns. However, complications such as localized and limited drug absorption in the wound, drug resistance, allergic dermatitis, burning, edema, erythema, itching, and blisters have been reported. Due to these complications, researches are conducting to find less complicated and effective alternatives for the treatment of burns (12).

Aloe Vera is a clump-forming, perennial succulent with basal rosettes of tapering thick leaves. This plant has thick, juicy and coarse leaves. The middle of the leaves is filled with a high viscosity transparent gel (12-14). Aloe Vera gel contains collagen, which can enhance the tissue granules and its anti-inflammatory properties can be effective in the process of wound healing and epithelialization (15-17). The anti-inflammatory effect of Aloe Vera is due to the existence of salicylic acid and
Arachidonic acid (18). Salicylic acid inhibits the production of Bradykinin and histamine. Arachidonic acid inhibits prostaglandin production (19, 20). Research has shown that Aloe Vera has bacteriostatic and bactericidal effects on species such as Pseudomonas Aeruginosa, Escherichia coli, Salmonella Typhi and Mycobacterium tuberculosis (9). One in vitro studies has shown that Aloe Vera accelerates wound healing up to 40% (21).

Recovery of burns is a long and painful process that causes the suffering of the patient and the family and imposes substantial costs on them. Second-degree burns require 3-4 weeks to recover. Decreasing recovery time can reduce patient suffering and the cost of treatment (22). Second-degree burns are the most painful types of burns. Treatment for this type of burn should be done with minimal skin irritation. As the Aloe Vera, in addition to its antimicrobial properties, has the effect of moisturizing and reducing irritation, it can be an excellent ingredient for second degree burns dressing. The aim of this study was to evaluate the effectiveness of Aloe Vera mucilage in the recovery of superficial second-degree burns. We compared aloe Vera with 2% Nitrofurazone Ointment as a routine and recommended treatment for superficial second-degree burns. Study hypothesis is the Aloe vera gel accelerates recovery healing of superficial second-degree burns

Methods
This study was a randomized split body controlled clinical trial. The study population consisted of all outpatients with superficial second-degree burns who attended to Shafa hospital burn center, Kerman, Iran. A convenience sample of 30 patients who had inclusion criteria enrolled in the study. Inclusion criteria were having two superficial second degree burns with one burn positioned on the one side of the body and the other positioned on the alternate side of the body, total burns less than 20% of the body, each burn surface smaller than 16 cm, no sign of infection and prescribing 2% Nitrofurazone Ointment by Physician, no need for hospitalization, having physician permission to use Aloe Vera Gel instead of 2% Nitrofurazone Ointment, not being affiliated with underlying disease such as diabetes and immune deficiency such as cancer, AIDS and severe skin sensitivity and skin problems, the cause of the burn was contact with heat or hot liquids, admitting to the hospital before 6 hours, no material other than drinking water was used on the wound.
Random allocation was done by the study statistician. He prepared 30 envelopes containing 15 cards labeled R and 15 cards labeled L. Each Patient selected an envelope. If the envelope with the letter R was opened, interventions would be done on the right side of the body, and vice versa. The other side of the body was treated with 2% Nitrofurazone ointment. Wounds were washed daily with normal saline 0.9%. Dressings were changed on a daily basis (according to the routine of the hospital). The burned areas were evaluated for infection each day. Burn wound infection criteria were as detailed by the American Burn Association Consensus Conferences (including Change in color of the burnt area or surrounding skin, Purplish discoloration, mainly if swelling is also present, change in thickness of the burn (the burn suddenly extends deep into the skin), Greenish discharge or pus and Fever. Patients with signs of infection or Systemic Inflammatory Response Syndrome (SIRS) were excluded from the study. The wounds were assessed and dressed daily by the third author. Patients were followed up for three weeks afterward. At the end of each week, assessment tools (The Bates-Jensen Wound Assessment Tool) were completed for both the control and intervention areas. Sample recruitment and allocation are presented in figure 1. During the study, 7 patients were added to the research because the outflow of samples were higher than what was expected before.

Aloe Vera gel was extracted as 100% mucilage from the middle part of the Aloe Vera leaf. The Aloe Vera gel was extracted and sterilized by the Iranian Institute of Medical Plants. The intervention included the use of the Aloe Vera gel in the burn area in a form that covered the whole surface of the burn. Control areas dressed with 2% Nitrofurazone Ointment. The Third author who is a nurse with 5 years of work experience in burn center did generated the random allocation sequence and enrolled participants, and assigned participants to interventions. all participant was blinded after assignment to interventions.

The Bates-Jensen Wound Assessment Tool (BWAT) was used to evaluate wound healing (23). It is a validated wound assessment tool which is used in many healthcare settings for wound assessment. BWAT is straightforward to use and allows nurses to have an objective, comprehensive assessment of wounds. It consists of 13 items to evaluate wound size, type and depth, amount of necrotic tissue, amount and characteristics of exudate, the presence of granulation tissue, epithelialization, and peri-
wound skin. The items and scoring are presented in table 1. Each item is graded on a scale of 1 to 5, where a score of 1 indicates progress toward healing while a score of 5 indicates the absence of healing or wound deterioration. Cumulative BWAT scores vary from 13 to 65 (24). Items and scoring of BWAT are presented in table 1. Two raters (third author and another nurse) scored all wounds simultaneously, the mean of two scores considered as BWAT score. The English version of BWAT has been reported to have good reliability (Cronbach alpha=0.91 and an interrater reliability coefficient of 0.99 (25, 26). Persian version of BWAT was used in previous studies (27). Twenty burns were assessed by two raters separately, and interrater reliability coefficient was 0.89.

Table 1- Items and scoring of Bates-Jensen Wound Assessment Tool

| Item                     | 1                      | 2                      | 3                      | 4                      | 5                      |
|--------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|
| Size (Length * width)    | <4 sq cm               | 4--<16 sq cm           | 16.1--<36 sq cm        | 36.1--<80 sq cm        | >80 sq cm              |
| Depth                    | Non-blanchable         | Partial                | Full thickness         | Obscured by            | Full thickness         |
|                          | erythema on            | thickness skin         | skin loss involving    | necrosis               | skin loss with         |
|                          | intact skin            | loss involving         | epidermis &/or         |                        | extensive destruction, |
|                          |                        | thickness skin loss    | dermis                 |                        | tissue necrosis or     |
|                          |                        | involving damage or    |                        |                        | damage to muscle, bone|
|                          |                        | necrosis of subcutaneous|                        |                        | or supporting         |
|                          |                        | tissue; may extend     |                        |                        | structures             |
|                          |                        | down to but not        |                        |                        |                        |
|                          |                        | through underlying    |                        |                        |                        |
|                          |                        | fascia; &/or mixed     |                        |                        |                        |
|                          |                        | partial & full         |                        |                        |                        |
|                          |                        | thickness &/or tissue  |                        |                        |                        |
|                          |                        | layers obscured        |                        |                        |                        |
|                          |                        | by granulation tissue  |                        |                        |                        |
| Edges                    | Indistinct, diffuse,  | Distinct, outline      | Well-defined, not      | Well-defined,          | Well-defined,          |
|                          | none clearly visible   | clearly visible,       | attached to wound      | not attached to base,  | fibrotic, scarred      |
|                          |                        | attached, even with    | base                   | rolled under,          | or hyperkeratotic      |
|                          |                        | wound base             |                        | thickened              |                        |
| Undermining              | None present           | Undermining < 2 cm in  | Undermining 2-4 cm     | Undermining 2-4 cm     | Undermining > 4 cm     |
|                          |                        | any area               | involving < 50% wound  | involving > 50% wound  | or Tunneling in any    |
|                          |                        |                        | margins                | margins                | area                   |
| Necrotic Tissue Type     | None visible           | White/grey non-viable  | Loosely adherent       | Adherent, soft,        | Firmly adherent, hard,|
|                          |                        | tissue &/or non-        | yellow slough          | black eschar           | black eschar           |
|                          |                        | adherent yellow slough |                        |                        |                        |
| Necrotic Tissue Amount   | None visible           | < 25% of wound bed     | 25% to 50% of wound    | > 50% and < 75% of     | 75% to 100% of         |
|                          |                        | covered                | covered                | wound covered          | wound covered          |
| Exudate Type          | None                  | Bloody                        | Serosanguineous: thin, watery, pale red/pink | Serous: thin, watery, clear | Purulent: thin or thick, opaque, tan/yellow, with or without odor |
|-----------------------|-----------------------|-------------------------------|---------------------------------------------|-----------------------------|---------------------------------------------------------------|
| Exudate Amount        | None, dry wound       | Scant, wound moist but no observable exudate | Small                                      | Moderate                    | Large                                                          |
| Skin Color            | Pink or normal for ethnic group | Bright red &/or blanches to touch | White or grey pallor or hypopigmented       | Dark red or purple &/or non-blanchable | Black or hyper-pigmented                                       |
| Surrounding Wound     |                        |                               |                                             |                             |                                                               |
| Peripheral            | No swelling or edema  | Non-pitting edema extends <4 cm around wound | Non-pitting edema extends >4 cm around wound | Pitting edema extends < 4 cm around wound | Crepitus and/or pitting edema extends >4 cm around wound |
| Tissue Edema          |                        |                               |                                             |                             |                                                               |
| Peripheral            | None present          | Induration, < 2 cm around wound | Induration 2-4 cm extending < 50% around wound | Induration 2-4 cm extending > 50% around wound | Induration > 4 cm in any area around wound |
| Tissue Induration     |                        |                               |                                             |                             |                                                               |
| Granulation Tissue    | Skin intact or partial thickness wound | Bright, beefy red; 75% to 100% of wound filled &/or tissue overgrowth | Bright, beefy red; < 75% & > 25% of wound filled | Pink, &/or dull, dusky red &/or fills < 25% of wound | No granulation tissue present |
| Epithelialization     | 100% wound covered, surface intact | 75% to <100% wound covered &/or epithelial tissue extends >0.5cm into wound bed | 0% to <75% wound covered &/or epithelial tissue extends to <0.5cm into wound bed | 25% to < 50% wound covered | < 25% wound covered |

The data was entered into SPSS Version 16. The BWAT scores reported as mean ± SD. The Shapiro-Wilk test was used to test for normality (p>0.05). The change in BWAT scores within each group was tested by repeated measure ANOVA. The paired sample t-test was used to compare the BWAT scores between two zones before, one, two and three weeks after intervention. Sample size was determined with this formula:
\[
\alpha = 0.05 \\
\beta = 0.2 \\
Z_{1-\alpha/2} = 1.96 \\
Z_{1-\beta} = 1.64 \\
\sigma_1 = 0.524 \\
\sigma_2 = 0.516
\]

d=0.69

\[
n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2(\sigma_1 + \sigma_2)^2}{d^2} = \frac{(1.96 + 1.64)^2(0.524 + 0.516)^2}{0.69^2} \approx 29.44 \cong 30
\]

Results

In the end, the burns of thirty patients who entered the study were analyzed. The mean and standard deviation of the age of the study units were 38.23 ± 15.02 years. Sixteen (53.3%) of the units were women. Seventeen participants were diploma and under diploma (56.7 %) and thirteen participants had a college degree (43.3 %). Sixteen participants (53.3 %) were single, and fourteen participants were married (46.7 %). The mean ± SD of burn diameter in Aloe Vera and Nitrofurazone zones were 26.2 ± 0.63 mm and 25.8 ± 0.62 mm, respectively (t=1.753, df= 28 p=0.09, CI: -0.12 to 1.40). BWAT scores were not significantly different between the two methods before and one week after the intervention. The difference in BWAT scores between the two groups was significant in the second and third weeks. The BWAT scores within two groups significantly decreased over time (Table 2).

Table 2- The comparison of BWAT scores between and within two groups

| Group         | Time | T1             | T2             | T3             | T4             | Repeal F | \( F(2, \ =440) \) | \( F(1, \ =228) \) |
|---------------|------|----------------|----------------|----------------|----------------|-----------|-------------------|-------------------|
| Aloe Vera     | 30.32 ± 3.28 | 27.33 ± 3.38 | 21.33 ± 3.13 | 16.12 ± 2.16 |                |           |                   |                   |
| Nitrofurazone | 30.51 ± 3.79 | 28.45 ± 3.49 | 23.36 ± 2.89 | 19.23 ± 2.11 |                |           |                   |                   |
| t-test        | t=-0.20, df=58, p=0.41, CI= -2.02 to 1.64 | t=-1.26, df=58, p=0.10, CI= -2.89 to 0.65 | t=-2.61, df=58, p=0.006, CI= -3.59 to -0.46 | t=-5.64, df=58, p=0.001, CI= -4.21 to -2.00 | |

Discussion

The results of this study showed that burns were improved on both Aloe Vera and nitrofurazone zones. The wound healing was significantly faster in zones that were dressed with Aloe Vera gel. This result is compatible with the results of previous studies.

The probable cause of the effectiveness of the Aloe Vera gel is that there are certain polysaccharides in it (28). These glycoproteins contain polysaccharides that stimulate the recovery of the skin. Aloe
Vera also has a compound called glucomannan, a polysaccharide which has mannose. Glucomannan affects fibroblasts growth factor receptors and stimulates the activity and proliferation of these cells. This increases the production and secretion of collagen. Aloe Vera mucilage, in addition to increase the amount of collagen in the wound, modifies its structure. Increasing cross-connections between collagen strands accelerates wound healing (29). Aloe Vera dressing is classified in the category of wet dressings due to the presence of hydrocolloids (30). Several studies have shown that wet dressings provide an ideal environment in regards to moisture and temperature for wounds (31). Moisture increases the production of collagen and accelerates the formation of blood vessels, epithelialization and the formation of granular tissue (32). Wet dressings can double the speed of wound healing because the wet environment allows fibroblast cells to immigrate faster to the epidermis and accelerate the recovery process (33). Aloe Vera also has lysine; lysine helps with wound healing by removing toxic substances, increasing blood flow and removing dead cells (34). The results of this study are consistent with the conclusion of a review study that showed that Aloe Vera gel accelerates burns recovery in superficial grade one burns (35). Studies on wounds such as pressure ulcers, diabetic wounds, cesarean section, and episiotomy showed that the Aloe Vera gel was effective in wound healing (36-41). Comparison of the effect of Aloe Vera gel and 1% silver sulfadiazine cream on the recovery of grade 2 burns showed that the Aloe Vera Gel improves the wound more rapidly (27). The results of another study showed that dressing with Aloe Vera gel was also effective in improving deep burn wounds (42). High rate of sample loss and the fact that desirable blinding was not achievable, are two main limitations in this study.

Conclusion
Aloe Vera gel can be a good alternative for 2 % Nitrofurazone in the dressing of superficial second-degree burns. Aloe Vera accelerates wound healing and can reduce the treatment costs for patients and the health system. It can lead to the enhancement of quality of care.

Abbreviations
BWAT: The Bates-Jensen Wound Assessment Tool

Declarations
Ethics approval and consent to participate
The study protocol was approved by the Ethics Committees of the Tehran University of Medical sciences (TUMS). The trial is registered in the Iranian Registry of Clinical Trials (IRCT2014113020151N1). Before participation in the study, written informed consent was obtained from each participant. All of them could withdraw from the study whenever they desired. The information on all research units was confidential.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that there is no conflict of interests.

Authors' contributions

SV and HR wrote the manuscript draft, SV and PS designed the study and conducted the data gathering, SB and SA Conducted statistical analyses. All authors reviewed the final manuscript.

Consent for publication

Not applicable

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Figures
Study flowchart: recruitment and allocation to study groups

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