

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 2% Nitrofurazone ointment in the healing of superficial partial thickness burn wounds.

Methods: The present study was a split body controlled, randomized clinical trial. The sample was recruited from patients with superficial partial thickness burn wounds who were prescribed to treat with 2% Nitrofurazone ointment. Thirty patients with at least two burns, each burn on an alternate side of the body, entered the study – samples allocated to two areas 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 epithelialization parameter and sum score Bates-Jensen tools were evaluated before, one, two and three weeks after the beginning of treatment.

Results: The mean \pm SD of epithelialization parameter in Aloe Vera area were 5.0 ± 0.00 , 4.0 ± 46.57 , 3.0 ± 50.57 , 2.0 ± 56.62 . The mean \pm SD of epithelialization parameter in 2% Nitrofurazone ointment area were 5.0 ± 0.00 , 4.0 ± 66.54 , 3.0 ± 76.50 , 3.0 ± 03.61 . and The mean \pm SD of BWAT scores in Aloe Vera area 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 \pm SD of BWAT scores in 2% Nitrofurazone ointment area 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 epithelialization parameter and (BWAT) scores between intervention and control area. Based on this study it looks like that Aloe Vera gel could promote epithelialization and wound closure more effectively than 2% Nitrofurazone ointment.

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 (7).

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.

The American Burn Association (ABA) has published an educational resource that reviewed the classification and management of the burn wound. The classification system below is largely in agreement. Superficial or epidermal burns involve only the epidermal layer of skin. They do not blister but

are painful, dry, red, and blanch with. Partial-thickness burns involve the epidermis and portions of the dermis. They are characterized as either superficial or deep. Superficial partial thickness These burns characteristically form blisters within 24 hours between the epidermis and dermis. They are painful, red, and weeping and blanch with pressure. These burns generally heal in 7 to 21 days; scarring is unusual, although pigment changes may occur. A layer of fibrinous exudates and necrotic debris may accumulate on the surface, which may predispose the burn wound to heavy bacterial colonization and delayed healing. These burns typically heal without functional impairment or hypertrophic scarring. Deep partial thickness – These burns extend into the deeper dermis. Deep burns damage hair follicles and glandular tissue. They are painful to pressure only, almost always blister (easily unroofed), are wet or waxy dry. Full-thickness – These burns extend through and destroy all layers of the dermis and often injure the underlying subcutaneous tissue. Extension to deep tissues – Fourth-degree burns are deep and potentially life-threatening injuries that extend through the skin into underlying soft tissue and can involve muscle and/or bone (8).

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 partial thickness burns is daily washing and dressing with 2% Nitrofurazone ointment (10). 2% Nitrofurazone ointment is a topical anti-infective agent which is effective against gram-negative and gram-positive bacteria (11, 12) . 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, renal impairment, thrombocytopenia, 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 (13-19). 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 (20, 21). 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 (22-24)The anti-inflammatory effect of Aloe Vera is due to the existence of salicylic acid and Arachidonic acid (25). Salicylic acid inhibits the production of Bradykinin and histamine. Arachidonic acid inhibits prostaglandin production (26, 27) Research has shown that Aloe Vera has

bacteriostatic and bactericidal effects on species such as *Pseudomonas Aeruginosa*, *Escherichia coli*, *Salmonella Typhi* and *Mycobacterium tuberculosis* (28). The results study showed that aloe vera be effective in shortening the duration of wound healing in superficial partial thickness burns(29-31), and it tended to increase rate of success to healing and rate of epithelialization (32) .

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. superficial partial thickness burns generally heal in 7 to 21 days. Decreasing recovery time can reduce patient suffering and the cost of treatment (33). superficial partial thickness 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 superficial partial thickness burns dressing(34).

Therefore the purpose of this study was to compare the effect of Aloe vera gel and conventional treatment (2% Nitrofurazone ointment) on healing of superficial partial thickness burns.

Methods

2.1. Study Design

This study was a randomized split body controlled clinical trial. The study population consisted of all outpatients with superficial partial thickness burns who attended to Shafa hospital burn center, Kerman, Iran.

2.2. Subjects and setting

A convenience sample of 30 patients who had inclusion criteria enrolled in the study. Inclusion criteria were having superficial partial thickness 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. In this study, one of the Inclusion criteria is the similarity in total BWAT score in both intervention and control areas. Statistical studies on all BWAT parameters, before the study, shown that the homogeneity in these areas

Random allocation was done by the study statistician. researcher 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% and dressing with sterile gauze (Sterile gases had no secondary substances) In both intervention and control area a thin layer of gel and ointment was used to cover the whole wound, so about 15 to 20 grams was used based on the wound size. 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. Sample recruitment and allocation are presented in figure 1.

The primary outcome in this study achieve a replacement for 2% Nitrofurazone ointment in treatment of superficial partial thickness burns and promotion healing in superficial partial thickness burns.

The Bates-Jensen Wound Assessment Tool (BWAT) was used to evaluate wound healing (35). It is a validated wound assessment tool which is used in many healthcare settings for wound assessment. BWAT is straight forward 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 (36). Items and scoring of BWAT are presented in table 1. Two raters (First 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 (37, 38). Persian version of BWAT was used in previous studies (39), 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 erythema on intact skin	Partial thickness skin loss involving epidermis &/or dermis	Full thickness skin loss involving damage or necrosis of subcutaneous tissue; may extend down to but not through underlying fascia; &/or mixed partial & full thickness &/or tissue layers obscured by granulation tissue	Obscured by necrosis	Full thickness skin loss with extensive destruction, tissue necrosis or damage to muscle, bone or supporting structures
Edges	Indistinct, diffuse, none clearly visible	Distinct, outline clearly visible, attached, even with wound base	Well-defined, not attached to wound base	Well-defined, not attached to base, rolled under, thickened	Well-defined, fibrotic, scarred or hyperkeratotic
Undermining	None present	Undermining < 2 cm in any area	Undermining 2-4 cm involving < 50% wound margins	Undermining 2-4 cm involving > 50% wound margins	Undermining > 4 cm or Tunneling in any area
Necrotic Tissue Type	None visible	White/grey non-viable tissue &/or non-adherent yellow slough	Loosely adherent yellow slough	Adherent, soft, black eschar	Firmly adherent, hard, black eschar

Necrotic Tissue Amount	None visible	< 25% of wound bed covered	25% to 50% of wound covered	> 50% and < 75% of wound covered	75% to 100% of 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 Surrounding Wound	Pink or normal for ethnic area	Bright red &/or blanches to touch	White or grey pallor or hypopigmented	Dark red or purple &/or non-blanchable	Black or hyper-pigmented
Peripheral Tissue Edema	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
Peripheral Tissue Induration	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
Granulation Tissue	Skin intact or partial	Bright, beefy red; 75% to	Bright, beefy red; < 75% & > 25% of wound filled	Pink, &/or dull, dusky	No granulation

	thickness wound	100% of wound filled &/or tissue overgrowth		red &/or fills < 25% of wound	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

2.3. Interventions

Aloe Vera gel was extracted as 100% mucilage from the middle part of the Aloe Vera leaf, and sterilized by the Iranian Institute of Medical Plants. The intervention areas dressed with the Aloe Vera gel and the Control areas dressed with 2% Nitrofurazone Ointment. The first author who is a nurse with 5 years of work experience in burn center did all the dressings.

2.4. Statistical Procedures

The data was entered into SPSS Version 16. The BWAT scores and BWAT parameter reported as mean \pm SD. The Shapiro-Wilk test was used to test for normality ($p > 0.05$). The change in BWAT scores and BWAT parameter within each area was tested by repeated measure ANOVA. The paired sample t-test was used to compare the BWAT scores and BWAT parameter between two areas before, one, two and three weeks after intervention.

Results

The findings of this clinical study showed The mean and standard deviation of the age of the study units were 38.23 ± 15.02 years. (53.3%) of the units were women. (56.7 %) participants were diploma and under diploma and (43.3 %) participants had a college

degree. (53.3 %) participants were single. The mean \pm SD of burn diameter in Aloe Vera gel and 2% Nitrofurazone areas 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 areas before and one week after the intervention. The difference in BWAT scores between the two areas was significant in the second and third weeks. The BWAT scores within two areas' shows there is a statistical difference between wound closure in the two areas of control and intervention (Table 2 and figure 2).

In addition to comparing the sum scores derived from Bates-Jensen tools, individual parameters were also evaluated statistically in the two areas of 'control' and 'intervention'.

Comparative evaluation of Bates-Jensen epithelialization parameters in the second and third week revealed a significant statistical difference in the process of epithelialization in both aforementioned areas. (Table 3 and figure 3)

During the study, eight patients were excluded from the study. three of them did not come back for treatment and five patients had allergic reaction in the control area. Therefore, one of the medical staff who was blind to the objectives of the research was chosen to select eight other patients according to the entry criteria to be added to research

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

Time Area	Before intervention	First Week after intervention	Second Week after intervention	Third Week after intervention	Repeated Measure ANOVA
Aloe Vera	30.32± 3.28	27.33± 3.38	21.33± 3.13	16.12± 2.16	F(2, 65.07) =440.00, p=0.001
2%Nitrofurazone	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
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	

Table3: The Comparison of epithelialization parameter between two areas

Time Area	Before intervention	First Week after intervention	Second Week after intervention	Third Week after intervention
Aloe Vera	5.0±00.00	4.0±46.57	3.0±50.57	2.0±56.62
2%Nitrofurazone	5.0±00.00	4.0±66.54	3.0±76.50	3.0±03.61
Repeated Measure ANOVA	1.00	0.234	0.037	0.003

Discussion

According to this study, 2% Nitrofurazone and Aloe Vera gel both resulted in the healing of burn wounds. However, if the epithelialization parameter in Bates-Jensen tools in the two areas of control and intervention are compared, the progression of epithelialization in intervention area is better than the control area, in the second and third weeks. In spite of the fact that, both areas of control and intervention were studied on the same person and all environmental, physical and nutritional factors- influential in the healing process- were the same.

Also, comparing the sum score Bates-Jensen tools in both areas in second and third week, shows that the progression of wound closure in intervention area is better than the control area, in the second and third weeks. It looks like that aloe vera gel could promote burn wound healing more effectively than 2% Nitrofurazone ointment.

Alongside with a large number of studies stating that Aloe Vera improves (30, 40-43) and accelerates (44-46) the healing process and epithelialization, a study published in 2019, states that nitrofurazone drug class diminishes epithelialization of wounds (47).

Based on a detailed review of articles, the Aloe vera as a medicinal plant for skin wound healing is confirmed (17, 48). Another method for skin wound healing is membranous dressings. While previous studies have shown that membranous dressings are more effective in partial thickness burns, they are also more expensive and need extra education and equipment (49, 50).

Najafi et al. reported the cause of the effectiveness of the Aloe Vera gel is that there are certain polysaccharides in it (14). These glycoproteins contain polysaccharides that stimulate the recovery of the skin. Glycoprotein fraction is the major component of aloe vera to be involved in wound healing with cell proliferation and migration (51).

Also, many studies past shown that Aloe Vera has a compound called glucomannan (52, 53). Glucomannan affects fibroblasts growth factor receptors and stimulates the activity and proliferation of these cells. This increases the production and secretion of collagen (54). Collagen is the major protein in the extracellular matrix and provides strength and integrity to the dermis and other supporting tissues (54-56). Aloe vera mucilage enhances the production amount of collagen in the wound, modifies its structure. Increasing cross-connections between collagen strands accelerates wound healing (55, 56).

A study by Shahzad et al. showed that Thermal burns patients dressed with Aloe Vera gel showed advantage compared to those dressed with SSD regarding early wound epithelialization, earlier pain relief and cost-effectiveness (57). Another article revealed that aloe vera could be a treatment of choice for burn injuries (58). Hajhashemi proved evidences that topical application of aloe vera would improve of the healing wounds in rats (59). A clinical trial investigation reported that aloe vera and *Calendula* ointment improve the speed of episiotomy wound healing; therefore it could be considered for quickening the episiotomy healing (60).

In other hand Aloe Vera dressing is classified in the category of wet dressings due to the presence of hydrocolloids (34, 45). Several studies have shown that wet dressings provide an ideal environment in regards to moisture and temperature for wounds (61, 62). Moisture increases the production of collagen and accelerates the formation of blood vessels, epithelialization and the formation of granular tissue (63, 64). 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 (65, 66).

As well as Aloe Vera has lysine; lysine helps with wound healing by removing toxic substances, increasing blood flow and removing dead cells (67). The results of this study are consistent with the conclusion of a review study that showed that Aloe Vera gel promoted burns recovery(68) and promote Epithelialization Superficial or epidermal burns(69) . Studies on wounds such as pressure ulcers, diabetic wounds, cesarean section, and episiotomy showed that the Aloe Vera gel was effective in wound healing and Epithelialization (17, 44, 60, 70-72). Comparison of the effect of Aloe Vera gel and 1% silver sulfadiazine cream on the recovery of superficial partial thickness burns in human and animale showed that the Aloe Vera Gel improves the wound more rapidly (39, 73). The results of another study showed that dressing with Aloe Vera gel was also effective in improving deep burn wounds (68, 74). In this study the outflow of samples were higher than what was expected .this is one limitation in this study.

Conclusion

Based on this study it looks like that aloe vera gel could promoted epithelialization and wound closure more effectively than 2% Nitrofurazone ointment. therefor it can be said that patients visit the hospital less frequently for dressing changes, the risk of infection decreased hence, they can recover more quickly in their personal and social lives and decrease all cost treatment. And due to the systemic side effects of 2% Nitrofurazone ointment like renal impairment, thrombocytopenia, and allergic reactions, especially contact dermatitis and drug resistance, Aleo vera gel can be a good herbal alternative for 2% Nitrofurazone in superficial partial thickness burns. As researchers suggest, lack of comparative studies between Aleo vera and 2% Nitrofurazone, necessitates further studies with a larger number of samples.

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.

Consent to publish

Not Applicable

Availability of data and materials

All data will be available on request. Everyone can request the data. To gain access, data requestors will need to sign a data access agreement. The data is available for any purpose. All applications should be sent to Parichehr_sabaghzadeh@yahoo.com. All requests will be answered within a maximum of 1 month by email.

Competing interests:

The authors declare that they have no competing interests

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Competing interests

The authors declare that there is no conflict of interests.

Authors' Contributions

Investigation: SV, HR, PS, SB, SA

Methodology: SV, PS

Software: SV, HR

Supervision: SV

Writing – original draft: SV, HR, PS, SB, SA

Writing – review & editing: SV, HR, PS, SB, SA

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Figures

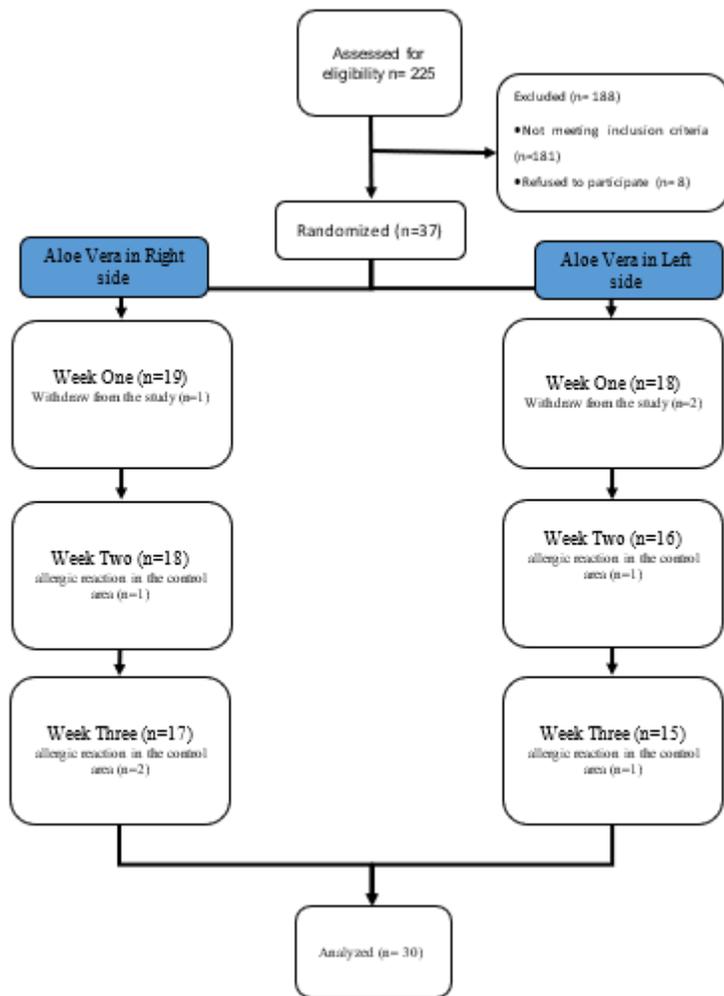


Figure 1

Study flowchart: recruitment and allocation to study areas

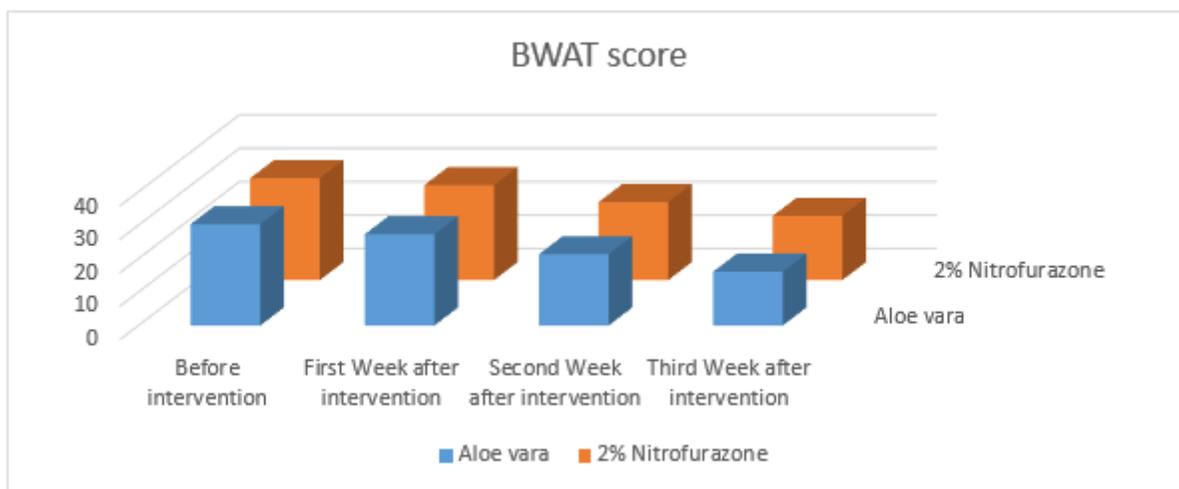


Figure 2

The comparison of BWAT scores between two areas

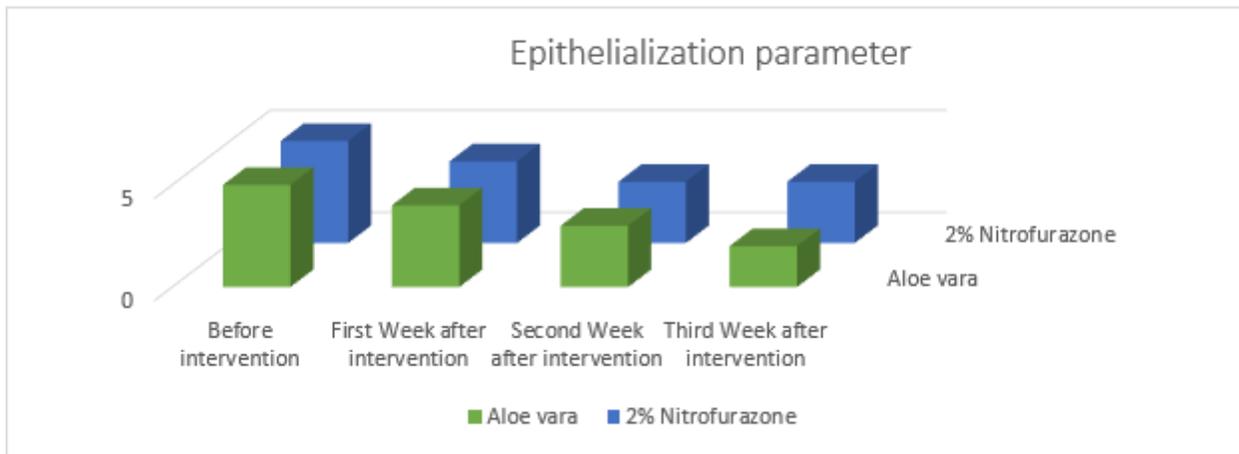


Figure 3

The Comparison of epithelialization parameter between two areas

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