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Aloe vera gel application for faster healing of split-thickness skin graft donor site on Wistar rats

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ABSTRACT

Background: Split Thickness Skin Graft (STSG) donor site healing still becomes concerned since it caused massive pain, discomfort, irritation, soaked, and thick dressing. None of the dressing can be said as the ideal and universal way to treat donor site. Aloe vera has been used as wound treatment, but the mechanism is not well understood yet. This study aims to determine the application of aloe vera gel to heal split-thickness skin graft donor sites on Wistar rats.

Methods: An experimental study was conducted among 32 male Wistar rats, 8-12 weeks age with STSG donor area divided into 4 control groups that treated with paraffin gauze and 4 groups that treated with *Aloe vera* gel. All wounds are closed by transparent dressing and being changed every 2 days. Healing time was count when all wound areas had epithelialization. In the microscopic evaluation, fibroblast, angiogenesis, and collagen deposition were counted on Day 5, 14, and 21. Data were analyzed using SPSS version 17 for Windows.

Results: Topical Aloe vera gel for STSG donor site treatment proved initiating significant faster epithelialization time (p=0.018), increasing the amount of fibroblast (p=0.006), and collagen deposition (p=0.001) on Day 5. However, topical aloe vera did not significantly affect the amount of angiogenesis in the early phase (Day 5) of wound healing (p=0.114) but proved to increase significantly in Day 21 (p=0.027).

Conclusion: Topical Aloe vera gel proved to heal the STSG donor site faster than paraffin gauze. Aloe vera can be used as one of STSG donor site treatment as it induces faster wound healing.

Keywords: Aloe Vera, STSG Donor, Paraffin Gauze. Faster Healing, Skin Graft
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INTRODUCTION

Split Thickness Skin Graft (STSG) is one of the procedures in the reconstruction ladder for defect closure, which is performed more than 160.000 times in a year.[1] This procedure will make another new superficial wound and make patients feel uncomfortable caused by more pain than the original wound, irritation, thick, heavy, and wet wound dressing.[1] STSG donor site has to be highly considered so it can heal completely and does not cause another new problem.[1] Previous research shows that 17% of the STSG donor site got complications, which will prolong the wound healing process, especially those who did not treat it by the moist wound dressing method.[2]

Ideal dressing of STSG donor site aims to reduce pain, induce epithelialization, prevent infection, minimal scar, safe, cheap, and easy to find.[1,2] Wound healing is a complex process and any medical interventions aim to promote faster recovery.[1] Aloe vera is an herb that already been used for wound treatment since ancient times.[3] Aloe vera has about 75 components, including amino acids, vitamins, minerals, and water. Aloe vera reduces inflammation by inhibiting IL-6 and IL-8, increase IL-10, reduce leukocyte adhesion, and decrease TNF alpha.[3] Aloe vera also contains glucomannan, which is rich in polysaccharides that stimulate fibroblast proliferation, angiogenesis, and increase collagen synthesis. Additionally, it has 99% of the water that moisture the wound.[4]

Aloe vera is believed for its anti-inflammatory, anti-bacterial, antiseptic, anti-viral moisture and contain wound healing induces components.[5] Based on those mentioned above, this study aims to evaluate the application of aloe vera gel for the healing of split-thickness skin graft donor sites on Wistar rats.

METHODS

Experimental animals

This is an experimental study with healthy and active 32 male Wistar rats, 8-12 weeks old, weighing 150-200 grams. Rats were put in standard cages with controlled room temperature (20-25°C) and humidity (65-75%). They were being observed by

a veterinarian and fed with fat chow and tap water. In addition, the rats were also treated based on the ethical principles for animal experiments of the international council for animal protection. Thirty-two rats were divided randomized into 8 groups (4 control groups were treated with paraffin gauze, and 4 experimental groups were treated with topical gel Aloe vera) which 2 groups for epithelialization time, 2 groups for day 5 amount of fibroblast, angiogenesis, and collagen deposition, 2 groups for day 14 amount of fibroblast, angiogenesis and collagen deposition and 2 groups for day 21 amount of fibroblast, angiogenesis and collagen deposition.

Aloe vera gel preparation

Aloe vera barbadensis leaves were cut, rinsed, and skin peeled off. The mucilaginous part was cut into small cuts, blender, and dried. Aloe vera was extracted with the maceration method, using 96% ethanol. Aloe vera gel extract was transformed into the gel using carbopol 1%. The gel was being made by mixing 1gram carbopol, Aloe vera extract 20% and add until 100 ml aquades. The gel was applied to the donor site with a dose of 2 mg/cm^2.

Wound creation and assessment

Rats were anesthetized with xylazine 2% (5 mg/kg) and ketamine 10% 20 mg/kg. Back skin was shaved and STSG wound was created by silver dermatome knife in 2x1 cm size. The control groups' donor site was treated with paraffin gauze and transparent dressing; otherwise, experimental groups were treated with Aloe vera gel and transparent dressing. The dressing was changed and photographed every 2 days.

The donor site was evaluated, complete healing was noted as all the wound surfaces were epithelialized. Microscopic parameters, amount of fibroblast, angiogenesis, and collagen deposition, were assessed by donor site resection on days 5, 14, and 21. All microscopic parameter samples were colored with Hematoxylin-Eosin.

Statistical analysis

Mann Whitney was used to evaluating the significant difference in epithelialization time between control and experimental groups. An independent T-test was used to assess the significant differences in fibroblast, angiogenesis, and collagen deposition between control and experimental groups. Data were analyzed using SPSS version 17 for Windows.

RESULTS

This experimental study shows a significant difference (p<0,05) in epithelialization time between STSG donor sites treated with the application of Aloe vera gel than treated with paraffin gauze (Table 1). The results on day 5 show amount of fibroblast and collagen deposition had a statistically significant difference (p<0,05), that STSG donor sites treated with the application of Aloe vera gel were higher than those treated with paraffin gauze. But there was no significant difference in the amount of angiogenesis (Table 2).

The results on day 14 show amount of fibroblast, angiogenesis, and collagen deposition had a statistically significant difference (p<0,05), the STSG donor sites treated with the application of Aloe vera gel were more significant than treated with paraffin gauze (Table 3).

The results on day 21 show the amount of fibroblast, angiogenesis, and collagen deposition had a statistically significant difference (p<0,05). That amount of fibroblast on the STSG donor site treated with the application of Aloe vera gel was lesser than treated with paraffin gauze. The amount of angiogenesis and collagen deposition on the STSG donor site treated with the application of Aloe vera gel was higher than that treated with the paraffin gauze (Table 4).

Table 1. The time needed for epithelization on the STSG donor site.

Variable	Group	Day (Median-IQR)	p
Epithelialization	Paraffin gauze	12.50 (3.00)	0.018*
	Aloe vera	8.00 (2.00)	

Table 2. The number of fibroblasts, angiogenesis, and collagen deposition on STSG donor site at day 5

Variable	Group	Day	Amount (Mean±SD)	p
Fibroblast	Paraffin gauze	Day 5	30.50±5.80	0.006*
	Aloe vera		80.00±16.83	
Angiogenesis	Paraffin gauze		4.00±1.63	0.114
	Aloe vera		6.00±1.41	
Collagen deposition (%)	Paraffin gauze		56.54±6.40	0.001*
	Aloe vera		79.83±2.98	

Data are given as mean and standard deviation (SD) with significant value* p<0.05

DISCUSSION

Aloe vera is one of the pharmaceutical herbs that has been used in many conditions.[4,5] This study aims to prove the Aloe vera effect in wound healing, especially STSG donor site healing. It confirms the significant acceleration epithelial time on the STSG donor site by administering Aloe vera gel compared to paraffin gauze. This result is similar to a previous study in incisions wound treated with Aloe vera gel ware healed faster than treated with povidone-iodine.[6]

Table 3. The number of fibroblasts, angiogenesis, and collagen deposition on STSG donor site at day 14

Variable	Group	Day	Amount (Mean±SD)	p
Fibroblast	Paraffin gauze	Day 14	61.75±11.44	0.006*
	Aloe vera		84.75±6.02	
Angiogenesis	Paraffin gauze		4.00±1.82	0.042*
	Aloe vera		6.25±0.95	
Collagen deposition (%)	Paraffin gauze		67.92±82.91 %	0.003*
	Aloe vera		82.91±3.80%	

Data are given as mean and standard deviation (SD) with significant value* p<0.05

Table 4. The number of fibroblasts, angiogenesis, and collagen deposition on STSG donor site at day 21

Variable	Group	Day	Amount (Mean ± SD)	p
Fibroblast	Paraffin gauze	Day 21	61.75±11.44	0.031*
	Aloe vera		26.00±5.59	
Angiogenesis	Paraffin gauze		4.25±1.50	0.027*
	Aloe vera		7.00±1,15	
Collagen deposition (%)	Paraffin gauze		77.75±4.93 %	0.005*
	Aloe vera		88.47±0.87 %	

Data are given as mean and standard deviation (SD) with significant value* p<0.05

This study also shows the amount of fibroblast on days 5 and 14 on the STSG donor site treated with Aloe vera gel was higher than treated by paraffin gauze. Another previous study also shows incisions wound with Aloe vera gel administration had a higher amount of fibroblast.[7] Normally, in the wound healing process, fibroblast starts to appear on day 4 with a peak level at day 21. On the other hand, this study shows the amount of fibroblast in the experimental group at day 21 already decreased and lesser than the control group. This can be caused by the wound healing process is faster than the normal one. A former study also showed the same result, where burn injury treated with Chitosan film with fucoidan that proved to heal faster, amount of fibroblast was higher at day 7 and 14 and would decrease and lesser at day 21.[8] Macrophage, as a growth factor, activates PDGF and TGF-β for fibroblast proliferation.[9] Fibroblast will produce an extracellular matrix and fill the wound area to facilitate keratinocyte migration.[9] Aloe vera contains glucomannan, rich in polysaccharides mannose, acemannan, gibberellin, and many growth factors that will induce macrophages to stimulate fibroblast proliferation.[6]

This study shows no significant difference in angiogenesis between STSG donor sites treated with Aloe vera gel and paraffin gauze on day 5 but had a higher amount on days 14 and 21 in the experimental group. This finding is the same with another study that surgery wounds treated with Aloe vera on days 6 and 10 did not significantly differ in angiogenesis.[10] Another study also showed that open wound treated with Aloe vera on day 10 had not increased yet and would dramatically increase at day 20.[11] These may be caused by in wound healing process, angiogenesis start to appear on day 3-5.[12] Since the samples were taken at day 5, probably angiogenesis just started to appear so still no significant difference with the control group. Angiogenesis is controlled by many cytokines like FGF-2, which is a growth factor for fibroblast and VEGF.[9] Aloe vera stimulates VEGF and eNOS to activate angiogenesis. Acemannan in Aloe vera also increased oxygen consumption and angiogenesis in wound healing. ß-sitosterol in Aloe vera is also believed as an angiogenic factor that increases essential protein expression in angiogenesis like VEGF, VEGF receptor, Flk-1, von Willebrand factor, and laminin. These factors will increase endothelial proliferation and migration for angiogenesis.[13] This is proved by a study that ß-sitosterol induced angiogenesis in chorioallantoic membrane chicken embryo.[14]

Collagen deposition in this study shows STSG donor site treated with Aloe vera gel is more increase than paraffin gauze on days 5, 14, and 21. Protein synthesis and deposition start on the 4^{th}-5^{th} day after injury.[13] Fibroblast proliferation is really important in collagen synthesis for tissue regeneration, which will be maximum at 2-4 weeks and than turn to getting slower.[9] Acemannan in Aloe vera is polysaccharides contain 97% mannose and 3% glucose. Mannose binds to its receptor and activates TGF-β, which induces collagen synthesis. Saponin in Aloe vera also increases cellular procollagen type I expression in human dermal fibroblast culture.[15] Ascorbate is required for proline hydroxylation of proline in procollagen synthesis and hydroxyproline will stabilize the helical collagen structure.[16] Before study showed topical vitamin C on postmenopausal women skin, stimulated and increased collagen type I and III.[17]

Aloe vera can be used as a wound treatment since it induces wound healing by decrease inflammation and pain, stimulate fibroblast, collagen deposition, and proteoglycan that increase wound tensile strength to facilitate epithelialization. Aloe vera also contains antiseptic like lupeol, salicylic acid, nitrogen urea, phenol, and sulfur, which inhibit the virus, bacteria, and fungal growth.[18,19]

Conflict of Interest

The authors declare that there is no competing interest regarding the manuscript.

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Ethical Clearance

Ethics approval has been obtained from the Ethics Committee, Faculty of Medicine, Universitas Udayana, Bali, Indonesia, prior to the study being conducted.

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None

AUTHOR CONTRIBUTION

All of the authors equally contribute to the study from the conceptual framework, data gathering, and data analysis until reporting the study results through publication.

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