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Histhopathologic Evaluation of Curative Impact of *Aloe vera L.* Fresh Gel on Healing of Eexperimental Infected Full-Thickness Open Wounds Induced with *Staphylococcus aureus* in Dogs

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Abstract

Objective- to consider the influence of *Aloe vera L* fresh gel on healing process histopathologically.
Design- Experimental study
Animals- Five adult male mixed breed dogs aged 2-4 years
Procedures- Eight symmetrical full-thickness wounds were surgically created on the back of all five dogs under general anesthesia and sterile condition. After wound creation, 1 ml fluid containing 10^5 CFU of *S. aureus* was inoculated on each wound. Right wounds were covered with 1 ml *Aloe vera* fresh gel whereas the left wounds were not received any therapeutic material. Wounds' biopsies were assessed on days 7, 15, 21 and 28 in treatment and control groups.
Results- In microscopic examinations density of collagen fibers in the superficial (P = 0.039) and deep (P = 0.042) sections of 28-days old wounds were significantly higher in treatment group compared to control group. Also these fibers had more diameter and better alignment in treatment group. No significant differences ($P > 0.05$) were seen in other indices including fibrocytes, fibroblasts and inflammatory cells between treatment and control wounds.
Conclusions and Clinical Relevance- It seems that *Aloe vera* in addition to antibacterial effects, probably exerts its main effects on the characteristics of collagen fibers. These positive effects could cause the improvement of quality and quantity of collagen fibers and their structures.

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Introduction

Wound healing as a fundamental process to injury may be affected by many negative factors. Among these factors, infection is the most important cause which interferences with healing process.[1,2] Necessarily, presence of bacteria in wounds should not be defined as infection. A wound becomes infected when microorganism replicated and then induces a host defense mechanism with tissue damage.[1-4] This condition often occurs when bacterial numbers in a wound exceed 10^6 organisms per gram of tissue or per milliliter of exudate.[1] Bacteria with different mechanisms interrupt healing process: 1) Reduction the blood supplement and separation of wound edges due to presence of exudate and organisms as foreign bodies, 2) Attachment of bacteria to extracellular matrix (ECM) or releasing virulence factors such as enzymes and toxins, 3) of inflammatory phase due to increased cellular responses.[1-3]
Various bacterial species are capable to communicating with healing process but according to many studies, the commonest isolated bacterium from wounds is *Staphylococcus aureus*.[5] Although this species is an example of normal body flora in various species but when places in vulnerable regions such as wounds, can be converted to pathogen forms with infectivity capability, ranging from minor to more serious infections. Even some strains of *S. aureus* can be developed resistance form to commonly used antibiotics which limits range of effective antibiotics that are available.[4] With regard to the fact that incidence of infection would result in delayed healing and increasing of antibiotic resistance, prevention and treatment of infected wounds with suitable and harmless materials is necessary. Several natural products among plants and their derivatives have been revealed to accelerate the wound healing process. *Aloe vera* (*Aloe vera L.*, *Aloe barbadensis*) is a well-known plant with a variety of pharmacologic effects that continues to be traditionally used for the topical treatment of wounds, burns, acne, eczema, insect sting, and skin inflammation.[6-8] Carbohydrates are major components that make up 25% of the dry matter of *Aloe vera* gel.[6,8] Mannose 6-phosphate (M-6-P) and acetylated mannan (acemannan) are the most important mono- and poly-saccharide responsible for many therapeutic properties of *Aloe vera* gel. These two materials have specific receptors on different cells such as macrophages and fibroblasts.[1,7,9] Several mechanisms have been proposed for effectiveness of the inner jelly like material of *Aloe vera* (*Aloe vera* gel). Not only does *Aloe vera* gel creates a physical barrier upon wounds against external contamination, but also it can provide an appropriate environment for different stages of wound healing processes by means of its ingredients of vitamins, minerals, enzymes and amino acids in an aqueous media. Anti-oxidant, anti-inflammatory, anti-microbial, immunomodulatory properties and stimulant effects on proliferative phases such as fibroplasia, angiogenesis, epithelialization and collagen synthesis, are further possible mechanisms supposed for effects of this plant on wound healing.[7-13] Antibacterial properties of *Aloe vera* were evaluated in different studies. *S. aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Salmonella typhi*, *Streptococcus sp* and *Helicobacter pylori* are the most important bacterial species which *Aloe vera* can inhibits them.[14-16] In spite of various in-vitro studies, there are only a few investigations about effects of *Aloe vera* on infected wounds.[17] The present study is histopathologically evaluating the effectiveness of *Aloe vera* fresh gel on *S. aureus* infected skin wounds in dogs.

Materials and Methods

Experimental animals

Five adult male mixed breed dogs aged 2-4 years, weighing 30±5 kg (Mean±SD) were studied. Before study, complete clinical examination, hematological and biochemical blood analysis were performed for confidence of animal's health. Environmental disinfections, anti-parasitic treatment, rabies vaccination were also performed. The animals were kept in individual cages with water available and fed by standard feed. All the procedures in this study were approved by the animal ethics committee for studies on laboratory animals of the department of clinical sciences review Board at Faculty of Veterinary Medicine of Ferdowsi University of Mashhad in accordance to the Iranian community guidelines for laboratory animals and the principles of laboratory animal care (NIH publication NO. 86-23, revised 1985).

Wounds Creation

The animals were anesthetized with intramuscular injection of xylazine hydrochloride 2% (Alfazyne®, Alfasan, Woerden Holland) at the dose of 1 mg/kg body weight and ketamine hydrochloride 10% (Alfamine®, Alfasan, Woerden Holland) at a dose of 15 mg/kg body weight. First pair of full-thickness wounds measured 20 mm×20 mm were surgically created on the shoulder region of each dog with approximate 50 mm distance from mid line. In order to providing different-age wounds, further 3 pairs of wounds were caudally created at days 7, 13 and 21 of the study at a distance of 100 mm to each other. This wound creation method made animals with eight symmetrical wounds aged 7, 15, 21 and 28 days-old at the end of study. Immediately after wound creation, 1 ml fluid containing 10^5 CFU (ATCC 25923) *Staphylococcus aureus* was inoculated on each wound. After that, the wounds were covered with sterile vaseline gauzes (Paraffin gauze, Latif bandage & gauze Co, Iran) (Table 1).
After 72 hours, (day 3) to confirm the presence of bacteria and infection in the wounds, sterile swab sampling were performed from exudates of wounds for gram staining and inoculation on culture media.

Table1. Specification of wounds for both groups

CT(day)	ST(day)	WA(days)
0	28^{th}	28
7^{th}	28^{th}	21
13^{th}	28^{th}	15
21^{st}	28^{th}	7

CT, Wound creation and contamination days during study period;
ST, Sampling days during study period; WA, Wounds` ages.

Preparation of Aloe vera gel

Before performing study, the species of selected *Aloe vera* (*Aloe vera L.*) plant was approved by Herbaceous Sciences Research Center of Ferdowsi University of Mashhad. Anti-bacterial activity of the *Aloe vera L.* leaf gel was examined and confirmed against *S. aureus* in-vitro by Reference Bacteriology Labratory of Veterinary Faculty of Ferdowsi University of Mashhad. A fresh mature *Aloe vera* leaf was cut from the plant on each of the treatment days. Leaf was cleaned and disinfected by chlorine solution. The cuticle layer of the leaf was removed to expose the fillet layer (gel). This layer was homogenized in a sterile blender and then pasteurized under indirect heat at 65°C for 15 minuets.[18] The preparation method was used throughout study period.

Treatment protocol

The wounds in all animals were divided to 2 groups: right wounds as a treatment group and left ones as a control group. The wounds in the treatment group topically were received 1 ml of the prepared *Aloe vera* gel once daily according to treatment protocol and were covered with sterile vaseline gauzes whereas the control group did not receive any intervention except for changing of sterile gauze wound dressing on the same days. The first treatment was done at day 3 after bacteriological sampling. Treatments were continued according to below protocol:
28 days-old wounds: days 3, 4, 5, 6, 7, 8, 9, 11, 13, 15, 18, 21 and 24 of study period.
21 days-old wounds: days 10, 11, 12, 13, 14, 15, 16, 18, 20, 23 and 25 of study period.
15 days-old wounds: days 16, 17, 18, 19, 20, 21, 22, 24 and 26 of study period.
7 days-old wounds: days of study 24, 25, 26 and 27 of study period.
To avoid self trauma, animal bodies were covered with special designed clothes.

Histopathological evaluations

Under general anesthesia, the wound samples containing both healing and adjoin normal skin were collected at the end of study period (day 28) from both treatment and control groups. After fixation, paraffin sections of 5 µm thickness were stained by H&E and Masson's Trichrome (green) stains then examined by light microscopy at days 7, 15, 21 and 28. The criteria that were investigated, consists of inflammatory cells (white blood cells), fibrocytes and fibroblasts content that were evaluated by H&E stain and collagen fibers density that was studied by Masson's Trichrome stain. In every slide, 10 microscopic superficial and deep fields were randomly selected and the density of each of the criteria in each of the fields was scored among 0-5. Then the mean of obtained numbers in superficial and deep sections were calculated independently and were used for statistical analysis.

Statistical analysis

Wilcoxon signed-rank test was used to comparing the differences of histopathological parameters between treatment and control groups on each of days. A p value less than 0.05 was accepted as significant. All the data were analyzed with SPSS 16.0 (SPSS Inc, Chicago, IL, USA).

Results

In H&E stain, numerous inflammatory cells were accumulated in the superficial and deep regions in both treatment and control groups at day 7 whereas during later stages (days 21 and 28) tend to decrease. However, there was no significant difference between these two groups at days 7, 15, 21 and 28.

In evaluation of fibrocytes and fibroblasts cells in H&E stain, there was no significant difference between the treatment and control wounds at any days of study.

Collagen fibers content was studied with Masson's Trichrome. Density of collagen fibers in the superficial and deep sections were improved in treatment group compared to control group but in statistical analysis, there were only two significant increases in the collagen density in superficial ($P = 0.039$) (Table 2, Fig. 1) and in deep sections ($P = 0.042$) (Table 3, Fig. 2) at day 28. In descriptive evaluation of microscopic appearance of collagen fibers, treatment wounds had more thick fibers organized in a regular pattern in some superficial and deep sections compared to control wounds at day 28 (Fig. 3 and 4).

Table 2. Collagen Density of wound samples in superficial sections for both treatment and control groups at different days.

Days	Treatment Group		Control Group	
	Mean ± SD	Median	Mean ± SD	Median
7	0.8 ± 0	0.8	0.68 ± 0.17	0.7
15	0.94 ± 0.18	1	0.88 ± 0.21	1
21	2.52 ± 0.43	2.5	2.24 ± 0.32	2
28 *	2.60 ± 0.36	2.5	2.23 ± 0.25	2.3

* Statistical significance (P = 0.039) between groups.

Table 3. Collagen Density of wound samples in deep sections for both treatment and control groups at different days.

Days	Treatment Group		Control Group	
	Mean ± SD	Median	Mean ± SD	Median
7	1.54 ± 42	1.3	1.38 ± 0.25	1.3
15	1.74 ± 0.15	1.8	1.58 ± 0.29	1.4
21	3.00 ± 0.65	3.2	2.62 ± 0.62	2.2
28 *	3.44 ± 0.47	3.4	2.82 ± 0.55	3

* Statistical significance (P = 0.042) between groups.

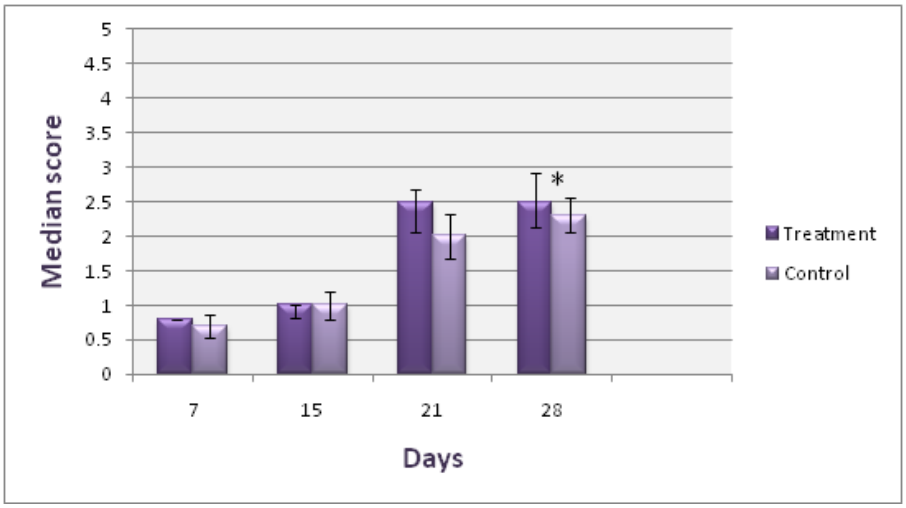

Figure1. Density of collagen fibers in superficial sections of wounds; The Density of collagen fibers in treatment group showed significant increase (*) in superficial section (P = 0.039) compared to control group at Day 28.

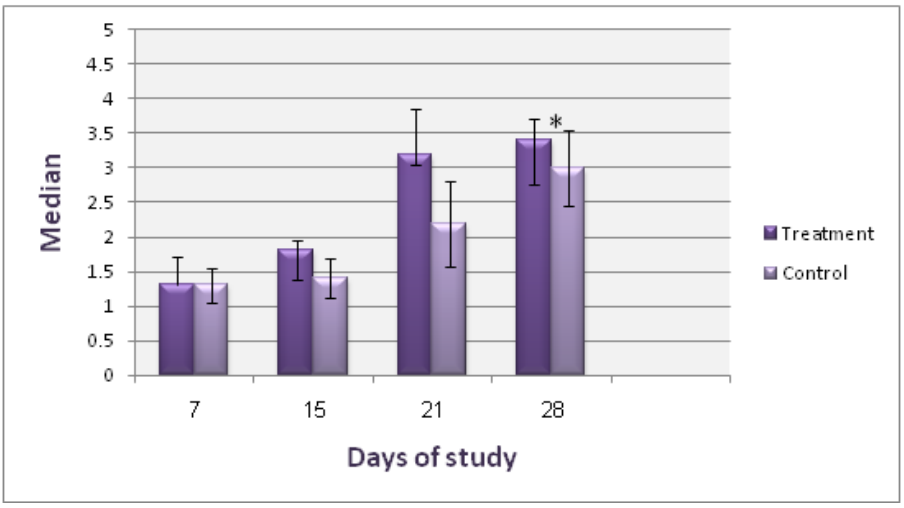

Figure 2. Density of collagen fibers in deep sections of wounds; The Density of collagen fibers in treatment group showed significant increase (*) in deep section (P = 0.042) compared to control group at Day 28.

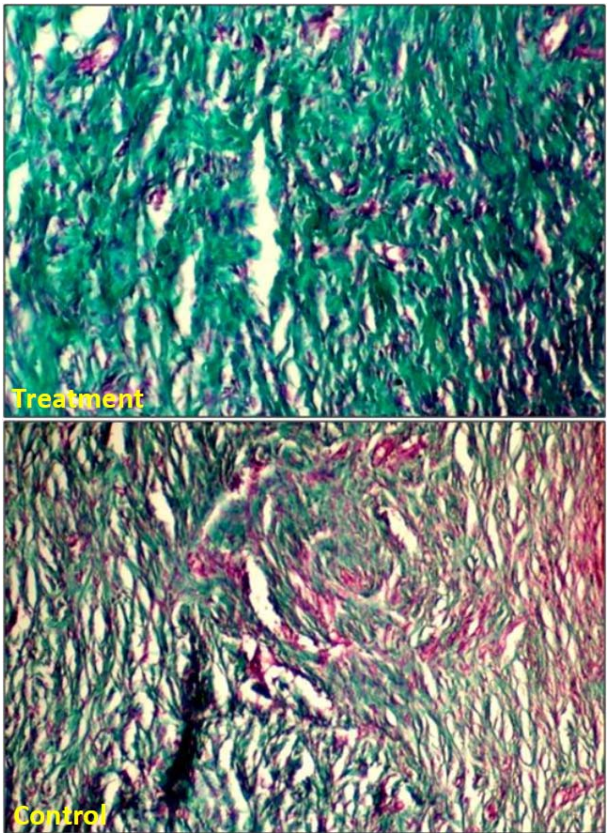

Figure 3. Histhopathological appearance of superficial sections of wounds at Day 28; More dense and thick collagen fibers in treatment group compared to lower content of collagen fibers in control group (Masson's Trichrome ×200).

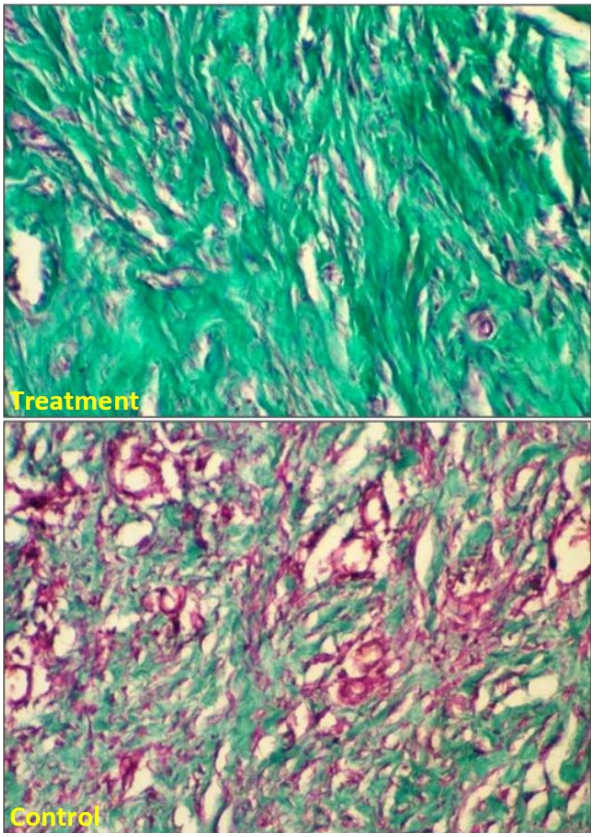

Figure 4. Histhopathological appearance of deep sections of wounds at Day 28; The higher density of collagen and thicker fibers with better orientation and organization in treatment wound compared to smaller density of collagen fibers with irregular pattern in control group (Masson's Trichrome ×400).

Discussion

In the present study effect of fresh *Aloe vera* gel was evaluated on healing process from two aspects: anti-inflammatory effect that investigated by assessment of white blood cells and impact of *Aloe vera* gel on proliferative phases that revealed by evaluation of fibrocytes, fibroblasts and collagen fibers density.

Results obtained from evaluation of inflammatory cells on all days of this study, did not show significant differences between two groups. Oryan et al (2010) reported reduction of inflammatory cells due to treatment of *Aloe vera*.[19] Apposite of this study, Leushbaug and Hale (1987) and Fei et al (2002) showed that *Aloe vera* gel increased numbers of inflammatory cells in the treatment of burn wounds at the primarily stages of wound healing process. It seems that this condition can be resulted in early elimination of necrotic tissue.[20, 21]

Fibroblast plays a key role in different stages of wound healing process especially the synthesis of collagen and other matrix proteins.[22] There are several experiments that reported *Aloe vera* and its most important component, acemannan, promote fibroblasts proliferation.[23,24] Davis et al (1989) determined that M-6-P and insulin-like growth factors II bind to the same receptor on fibroblast. This attachment can be stimulated fibroblast activity (9). Although Subramanian et al (2006) emphasized that positive effect of aloe vera on

fibroblast increases wound healing[23] but quantitative evaluation of fibrocytes and fibroblasts in the present study did not reveal significant improvement in treatment group compared to control group. These findings are parallel to Oryan et al (2010) results. They reported that *Aloe vera* did not affect fibroblast proliferation.[19] Different investigations about effect of *Aloe vera* on fibroblasts reveal a variation in achieved results may be due to complex interaction among *Aloe vera*, fibroblasts and their growth factors. It seems that different type of skin fibroblast can be effective in results. Abdullah et al (2003) reported that *Aloe vera* was able to increase gap junctions and proliferation of human type II diabetic skin fibroblasts whereas normal skin fibroblasts were not affected by *Aloe vera*.[25] Complementary experiment by Grazul -Bilska et al (2010) demonstrated that *Aloe vera* differentially affects on expression of fibroblast growth factor receptor 2 IIIc mRNA in human diabetic and non-diabetic skin fibroblasts.[26]

An important criterion that was investigated in the present study is collagen. Collagen has an important role in wound healing that contribute in different stages of healing such as homeostasis, ECM (extra cellular matrix) deposition, cellular signaling, migration and differentiation, wound contraction as well as providing integrity and strength of healed tissue.[27,28]*Aloe vera* is able to increase content of collagen fibers and improves their characteristics. These effects can arise indirectly via increasing activity of fibroblasts that responsible for collagen synthesis.[28] Complete evaluation of granulation tissue by Chithra et al (1998) revealed that topical application and oral administration of *Aloe vera* gel increased the collagen content as well as its degree of cross linking.[28] Histopathological evaluation of collagen fibers in this study showed that *Aloe vera* increased collagen content without specific effect on fibroblasts. Also these fibers were thicker and better oriented and organized result in more solidarity and tissue alignment in the final stage of healed wound. The results of current study are in accordance to results of several studies. Oryan et al (2010) reported that *Aloe vera* have no increasing effect on fibroblast proliferation, but improves the further maturation and alignment of fibroblasts and collagen fibers. So, these fibers have a greater degree of organized orientation.[19] Arijani and Khoswanto (2008) expressed that treatment with aloe vera accelerates the growth of collagen fibers and density of them.[29] Inan et al (2007) reported a higher level of hydroxyproline of *Aloe vera* treated rat both on the third and the seventh days that means higher collagen content.[30] In another study, Saberiafshar et al (2006) revealed that collagen fibers in wounds treated with *Aloe vera* were thicker and well arranged.[31] Also Parnell et al (2002) reported that wound treated with acemannan have thicker collagen fibers and deposition of them appear to be more evenly distribute.[32] Despite of existence of infectious wounds, concordance of results to other investigations` show that *Aloe vera* provides rapid maturation of collagen in addition to stimulation of collagen synthesis.[30] Infection as the most important extrinsic factor can lead to prolonged elevation pro-inflammatory cytokines such as IL-1 and TNF-α, destroying of ECM, stopping of needed proteins and molecules production for healing.[3] So these negative functions can be interrupted with *Aloe vera* activities. *S. aureus* is opportunistic pathogen that able to exert its destructive effects on wound healing by various mechanisms. It mainly produces a large number of virulence factors that Eap (extra cellular adherent protein) is one of the most important. This protein component has binding ability to various plasma molecule and ECM components such as fibronectin, collagen, elastin, epithelial and endothelial cells.[33,34] *S. aureus* could depress fibroblast proliferation in-vivo, as well as in-vitro.[35,36] Eap attenuates wound healing and consecutively develops chronic condition through increase of duration of inflammatory phase and of anti-angiogenesis property.[34,37] Despite of approved anti-bacterial effect of *Aloe vera* gel on *S. aureus* in several studies, Cock et al (2000) observed no anti-bacterial activity of

Aloe vera gel against this microorganism in-vitro.[38] Despite of no evidence of influence of *Aloe vera* on proliferation of fibroblast and fibrocyte in current study, it can affect characteristic of collagen fiber especially on last days of healing period. These effects conclude qualitative and quantitative improvement of collagen fibers and their structures. The variation in results of different studies may associate with several factors such as variation in amount of ingredients of *Aloe vera* as well as its processing methods.
In conclusion, *Aloe vera* has positive effects on *S. aureus* infected full-thickness wound healing of dogs according to our study. Finally, we recommend further investigations to evaluate the effectiveness of ingredients of *Aloe vera* on infected wounds healing process.

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چکیده

ارزیابی هیستوپاتولوژیک اثر درمانی ژل تازه الوئه ورا ال بر التیام زخم پوستی تمام ضخامت باز عفونی شده با استافیلوکوکوس آرئوس در سگ ها

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هدف- مطالعه حاضر جهت بررسی هیستوپاتولویک اثر درمانی ژل تازه برگ گیاه الوئه ورا ال بر روند التیام زخم پوستی انجام شد.

طرح مطالعه- مطالعه تجربی بر روی حیوان زنده

حیوانات- پنج قلاده سگ نر از نژاد مخلوط در محدوده سنی ۲ تا ۴ سال

روش کار- در این مطالعه دو سری زخم چهار تائی متقارن برروی پشت حیوانات، در دو طرف ستون فقرات در روزهای مختلف، تحت بیهوشی ایجاد شدند و سپس زخم ها توسط یک میلی لیتر مایع حاوی 10^5 CFU استافیلوکوکوس آرئوس تلقیح شدند. زخم های سمت راست توسط یک میلی لیتر از ژل آلوئه ورا ل پوشانده شدند در حالیکه زخم های سمت چپ هیچ درمانی را دریافت نکردند. بررسی روند التیام به صورت میکروسکوپی برروی بیوپسی های اخذ شده از زخم های هر دو گروه در روزهای ۷، ۱۵، ۲۱ و ۲۸ انجام شد.

نتایج- معنی داری برتری تراکم رشته های کلاژن در مقاطع سطحی ($P=0.039$) و مقاطع عمقی ($P=0.042$) هیستوپاتولوژی بدست آمده از زخم های روز ۲۸ در گروه درمان در مقایسه با گروه کنترل مشهود بود. همچنین ضخامت و نظم قرارگیری این رشته ها در گروه درمان بهتر بود. دررابطه با سایر شاخص ها مانند تعداد فیبروبلاست ها، فیبروسیت ها و سلول های آماسی تفاوت معنی داری ($P > 0.05$) بین دو گروه درمان و کنترل وجود نداشت.

نتیجه گیری و کاربرد بالینی- به نظر می رسد که آلوئه ورا علاوه بر داشتن خاصیت آنتی باکتریال، اثراصلی خود را برروی زخم از طریق تغییر خصوصیات رشته های کلاژن اعمال می کند که باعث بهبود کمیت و کیفیت رشته های کلاژن و ساختار آنها می شود.

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