Scientific Journal of Medical Sciences
Volume 1, Issue 3, Summer 2022
Pages: 107-111
Type: Descriptive Study

Comparing the Effects of Acticoat and Silver Sulfadiazine on Burn Wound Healing: A Randomized Comparative Trial between Acticoat and Silver Sulfadiazine in Burn Wounds Healing

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Abstract

Aims: Silver-containing dressings are the latest and biggest invention in wound care products. There are many dressing materials available to treat burn wounds but none of them has strong evidence to support their use. This study was done to compare the efficacy of nanocrystalline silver (Acticoat) and silver sulfadiazine (SD-Ag) in the treatment of burn wounds.

Instrument & Methods: This clinical trial was done in Arak city. Sixty-nine burn patients were enrolled and divided into two groups of the Acticoat group and silver sulfadiazine group. Acticoat was changed once every 3 days. Silver sulfadiazine was used as control group whose members were treated under the usual clinical routine. Healing time was observed up to 15 days. Healing percentage was determined on the 15th day after treatment.

Findings: By comparing the mean values of the size of the wound in three turns, it was observed that the size of the wound significantly decreased over the difference of the size between the two groups ($p=0.000$, $F=143.716$).

Conclusion: Acticoat with nanocrystalline silver promotes the healing process of wounds post-burn effectively. No adverse reaction of Acticoat was observed during the study.

Keywords
Wound Healing [https://www.ncbi.nlm.nih.gov/mesh/68014945];
Dressing [Not Found];
Acticoat [https://www.ncbi.nlm.nih.gov/mesh/?term=Acticoat];
Bandages [https://www.ncbi.nlm.nih.gov/mesh/68001458]

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Received: September 16, 2021 Accepted: February 20, 2022 ePublished: March 15, 2022

Introduction

Burns are a major public health problem in developing countries [1]. Sever burn injuries a dramatic event: deramatic in its inception in the flaming home, in an industrial accident, in the hands and action of an abuse adult [2] .The final goal of burn management and therapy is wound healing and epithelization as soon as possible to minimize infection and to reduce functional and aesthetic outcomes [3]. Treatment of partial thickness burn wounds is directed towards promoting healing, and a wide variety of dressings are currently available [4]. For centuries, silver has been used to treat burns and chronic wounds [5]. In the 19th century, silver nitrate was used to remove granulation tissue, therefore allowing epithelization, and to promote crust formation on the surface of the wound for large surface wounds that healed by epithelization from the edges and contraction [6]. Silver nitrate causes a significant amount of staining of virtually any surface with which it comes into contact [7] and can also cause irritation to tissues. In 1968, silver nitrate was combined with sulfonamide to form silver sulfadazine cream (SD-Ag) which served as a broad-spectrum antibacterial agent and was used for the treatment of burns. SD-Ag is effective against bacteria like *E. coli, S. aureus, Klebsiella* sp., *Pseudomonas* sp. It also possesses some antifungal and antiviral activities [8]. However, these conventional dressings tend to adhere to the wound surface [9] and their need for frequent changes results in damage to newly epithelialized surfaces and delayed healing. SD-Ag cream itself is also thought to delay wound healing due to a toxic effect on regenerating keratinocytes [4]. Inactivation of much of the silver by wound fluid and (in the case of SD-Ag) the formation of a pseudo-eschar are limited in the clinic. Complexes in wound fluid, additional silver is released, thus producing a sustained, steady supply of active silver [10]. The limitations of conventional dressings, improvements in technology and advances in our understanding of wound healing have led to an enormous expansion in the range of dressing options that can be used on burns. Burn wounds may lose large amounts of fluid through evaporation and exudation. Thus dressings must absorb fluid and maintain a high humidity at the wound site to improve granulation tissue formation and enhance re-epithelialization. The burn dressing should provide a bacterial barrier to prevent infection entering the wound or being transmitted from the wound. Burn dressings should also possess mechanical characteristics to improve movement [11]. Acticoat (Smith & Nephew, Hull, United Kingdom), is made up of two layers of polyamide ester membranes covered with nanocrystalline silver ions and a core absorption layer in the middle [11]. Results from clinical studies indicate that nanocrystalline silver dressings induce major improvements in the healing of a variety of wounds. In addition, the nanocrystalline silver dressings have been demonstrated to increase the rate of re-epithelialization across partial-thickness burns, and there are very positive results regarding their antimicrobial effectiveness and ease of use [12–15]. This kind of treatment is new in Iran and the world and its different aspects are unknown and there are no studies in this area in Iran. Hence, in the present study, we compared the effect of nanocrystalline silver (Acticoat) dressing and SD-Ag on burn wound healing.

Instrument and Methods

This randomized controlled trial was conducted in burn clinic of ValiAsr Hospital, Arak. Sample size was calculated according to the results of a previous study. Accordingly, with a type I error of 0.05 and a power of 0.80, the sample size calculation formula showed that 56 patients were needed for the study (Figure 1).

Two instruments were used to collect data. The first instrument was a demographic and burn -related questionnaire comprised of items such as age, gender, marital and educational status, burn depth, burn size (burn depth was assessed according to the "Three Degrees Categories Method", and the size of the burn was determined according to the "Lund and Browder chart"). The second instrument was the wound diagnostic tool-Bets's Jensen. This scale had a questionnaire of 15 phrases in which two phrases of place and the figure of the wound did not categorize but 13 other phrases were consisted of 5 parts according to Likert scale. Marks of questions were from one to five. The least mark 1 showed the best condition and the highest mark 5 indicated the worst condition. The least mark was 13 and the most one was 65.

A randomized experimental design was adopted, with blinding and positive parallel control.

The observing doctor handed out the dressing to every patient according to the time that they come to the hospital and to a randomized serial number. A nanocrystalline silver dressing (commercial name Acticoat, registration certificate number: SFDA 20043640127, made by Smith & Nephew Co. Ltd., UK), was used to cover the wounds of the trial group. Silver sulfadiazine (SD-Ag, a mass fraction of 1%, approval document number: national medicine approval number: Z1202440) was used as control group. After washing and rinsing the wounds of both the treated and the control groups with sterilized distilled water, Acticoat or SD-Ag were applied to the wounds. For those who had redness, swelling, and excessive secretion ("heavy" exudates) in the wound, the medicine was changed once a day. When there was not much secretion in the wound, and redness and swelling were not obvious, the medicine was changed once every 3 days. In the treated group, Acticoat was cut into pieces according to the size and

shape of the wounds, the pieces of Acticoat were placed in distilled water till it gets wet, then covered on the wound with the blue side downward. The Acticoat was covered with an auxiliary dressing on the top. The control group was treated with SD-Ag and changed daily. The experiment was terminated when the wounds were healed or after 15 days of medication.
All patients participated in the trial at their own volition. In-hospital patients, both males and females, with no serious complications of the heart, liver, kidney, blood system, and systemic infection were included in the study. Altogether, 69 patients were enrolled in the trial, which in the process of the trial, 5 patients were dropped out of the study. Among them 4 patients were dropped out because of wound infection, and one because of non- presence.
Patients who had a serious disease of the heart, liver or kidney, or had a blood producing disorder, an inclination to bleed or bleeding disease; shock or serious systemic infection; pregnant or breastfeeding women; those who had an allergic reaction to silver ions, and poor adaptively or seriously ill and could not finish the observation period, were excluded from the study. Patients who were found offending the requirements of the group in the process of the experiment; those who could not continue with the treatment due to certain reasons and had to finish the experiment, or those who could not finish all the test items due to certain reasons; those who met unexpected events during the treatment and had to stop therapy; those who annulled their agreement acknowledging their awareness of the conditions; and those who had serious complications/infections, were all removed from the trial. The wounds were observed dynamically in the process of medication. The secretion on the wound and the condition of the swelling, pain, etc., were recorded beginning of the study and every 7 days after the treatment. Photos were taken of all patients. The healing percentage in the wound and the healing time were observed and recorded: the healing percentage in the wound=((area before treatment- area after treatment)/area before treatment) 100%. The wound healed was determined by inspection by two doctors. Assessment and comments on the information of every patient and the efficacy of the medicine were created. The healing time of the wound was calculated as the number of the days for the healing of 100% of the wound. If the wound was not completely healed when the treatment period expired, the healing percentage of the wound was recorded.
The data were analyzed using the SPSS software version 16 (SPSS Inc., Chicago, IL, USA). Chi-square test was used to compare the ordinal and categorical data, repeated measures ANOVA was adopted to compare the average of continuous data, and Wilcoxon test was performed for comparing the healing percentage of the two groups. The results of statistical analysis were considered statistically significant at the level of <0.05.

Findings
Silver nanoparticles stimulate healing and result in better cosmetic outcome. In our clinical trial the healing time of the burn wounds in the experimental group (11.33±3.67) was shorter than that in the control group (17.68±5.45), on average 6.35 days shorter ($p<0.05$) and the difference of healing rate in the 15 days was significant between the two groups.
By comparing the mean values of the size of the wound in three turns, it was observed that the size of the wound significantly decreased over the difference of the size between the two groups ($p=0.000$, $F=143.716$). No local allergic or systemic symptoms were found. In 64 patients, no side effects were found relevant with the use of Acticoat (Tables 1).

Table 1) The average size of the wound in two groups (N=32)

Time	Group	Mean±SD	p
At the beginning	S-D	3.69±1.176	0.000
	Acticoat	3.53±1.191	
	p	0.000	-
On day 7	S-D	2.97±0.339	
	Acticoat	2.5±0.984	
	p	0.000	-
On day 15	S-D	1.84±0.808	0.000
	Acticoat	0	
	p	0.000	-

Discussion
The purpose of this study was to compare the effect of nanocrystalline silver (Acticoat) dressing and SD-Ag on burn wound healing.
In our clinical trial the healing time of the burn wounds in the experimental group was shorter than that in the control group, on average 6.35 days shorter ($p<0.05$) and the difference of healing rate in the15 days between the two groups was significant.
One possible explanation for this might be, the long wear time and the ease of application, and that the removal of Acticoat TM reduced trauma and time of wound healing. In addition, SD-Ag reacts with serous exudates to form a pseudo scar that must be removed before the cream can be reapplied. Acticoat TM can be left in place for up to 3 days, meaning that the wound does not have to be manipulated during this period, since it may cause trauma to the new epithelial growth and spread bacteria into the blood stream. The extended wear time of Acticoat TM dressings also means that the patient does not have to be moved or disturbed, which in turn could decrease pain and nursing time. This is particularly important for patients with burn and fractures. Similarly, Huang *et al.* found a decrease in healing time of burn wounds in the Acticoat TM group (3.35 days shorter, $p<0.01$) compared to the SD-Ag group in their multicenter RCT [16]. Demling and Desanti

showed a significantly increased rate of re-epithelialization when Acticoat TM was compared to antibiotic solution [13]. Burd *et al.* [17] conducted studies involving cell monolayers, tissue explants and animal models and suggested that Acticoat TM can delay the rate of wound re-epithelialization.

Other possible explanation for this might be that burn wounds, from a pathophysiological point of view, are at risk of developing infection [18], while the major roles of silver dressings in the management of wounds are to reduce bio burden and/or act as an antimicrobial barrier . As such, the prophylactic use of silver dressings in burns, as done in this clinical trial, is perfectly justified [19]. In fact, the main reason for applying dressings with antimicrobial properties in burn care is to avoid the problems associated with increased bacterial burden including delayed wound healing, prolonged hospital stay and increased costs and morbidity [20, 21]. In wound management, silver quantities should be sufficient to provide sustained bactericidal action. Acticoat TM with nanocrystalline silver provides the Ago form of silver, which is far less rapidly deactivated by chloride or organic matter than the ionic form [22]. As a nanocrystalline silver dressing, Acticoat displays a new state of silver—a combination of silver ion (Ag+) and active silver (Ag0). Whereas, regarding the SD-Ag, as a traditional therapy of silver, it is silver ions (Ag+) that work in the solution, and the silver ions released are not only combined with some compositions of the bacteria, but also combined with the protein in blood, or deposit due to its reaction with chlorine ions, which would disable the anti-bacteria capability of silver ions. Acticoat provides the wounds a dynamic active silver with a certain concentration. In some in vitro studies, it was found that nanocrystalline silver releases silver ions faster than SD-Ag, and bacteria disappear faster too [23]. In the skin grafting clinical experiment by Demling and DeSanti [13] in 20 burn patients, it was found that Acticoat can improve proliferation in the wounds. On the 7th day after the burn, the Acticoat group all healed, while in the group using antibiotics, only 55% healed.

Sustained release of silver is important in reducing bacterial burden but is also highly significant in terms of decreasing mechanical trauma. SD-Ag, which is a traditional therapy of silver, the negative ion compositions in its silver salt have some toxic effect to the tissues in the wound, which often cause prolonged healing of the wound. In this study, we find that as Acticoat is easy to be removed, patients have no complaint of obvious pain when changing the dressing. The secretion in the wound and swelling are obviously restrained. In the process of using Acticoat in this experiment, no definite systemic or local side effects are found.

Conclusion

This study suggests that Acticoat effectively improves the healing process of burn wounds. The application of Acticoat does not require frequent changing of the dressing and the changing of the dressing is convenient and simple. In addition, it does not cause much pain and patients do not suffer much from the medication. Thus, Acticoat seems to be a safer and better dressing for treatment of burn wounds.

Acknowledgments: The authors would like to thank all patients who agreed to take part in this research project.

Ethical Permissions: The study was approved by the Research Ethics Committee of Azad University of Medical Sciences, Thran, Iran (approval code: 123-88-234). Moreover, it was registered in the Iranian Registry of Clinical Trials (registration code: IRCT2012123111940N 2). Each participant signed a written informed consent at the time of recruitment to the study. They were assured of the confidentiality of their data as well as their ability to voluntarily withdraw from the study.

Conflicts of Interests: There are no conflicts of interest.

Authors' Contribution: Azam Malekhoseini (First author), Original Researcher (20%); Mohamad Rostamkhani (Second author), Assistant Researcher (20%); Golbarg Malekhoseini (Third author), Assistant Researcher (20%); Sina Abdeii (Fourth author), Assistant Researcher (20%); Siavash Abdii (Fifth author), Assistant Researcher (20%).

Funding/Support: This study was conducted at personal cost.

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