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Original Article

Nanocrystalline Silver Dressings in Comparison to Normal Saline Dressings in the Management of Lower Limb Ulcers

Arun Pandey[1], Aravind V Patil[2], Manjunath S Kotennavar[2], Rajendra Benakatti[3], Srajit Ranjan[4], Gourav Sandhu[4]

[1]Post-graduate Student (JR-3), Department of General Surgery, Shri B M Patil Medical College Hospital and Research Centre, Vijayapura, Karnataka, India, [2]Professor, Department of General Surgery, Shri B M Patil Medical College Hospital and Research Centre, Vijayapura, Karnataka, India, [3]Associate Professor, Department of General Surgery, Shri B M Patil Medical College Hospital and Research Centre, Vijayapura, Karnataka, India, [4]Intern, Department of General Surgery, Shri B M Patil Medical College Hospital and Research Centre, Vijayapura, Karnataka, India

Abstract

Aim and Objectives: This interventional comparative prospective study aimed to assess the effectiveness of nanocrystalline silver dressings versus normal saline dressings in managing lower limb ulcers, by comparing parameters such as reduction in ulcer surface area, the appearance of granulation tissue, reduction in slough, reduction in discharge, and culture sensitivity.

Materials and Methods: The study was conducted at BLDE DU Shri BM Patil Medical College Hospital and Research Center, Vijayapura, from January 2021 to October 2022, and involved 70 patients, divided equally between control (normal saline) and study (nanocrystalline silver) groups. Both groups received once-daily dressings for 2 weeks, and data on the above parameters were collected and compared.

Results: The study group (nanocrystalline silver) showed significantly better outcomes than the control group (normal saline). The study group exhibited a 57.63% mean reduction in ulcer surface area, compared to 27.09% in the control group. The study group also showed earlier reductions in wound discharge (31 out of 35 patients) and slough (33 out of 35 patients), the earlier appearance of granulation tissue (34 out of 35 patients), and greater potency against microorganisms.

Conclusion: Nanocrystalline silver dressings are highly effective in managing lower limb ulcers, with significant reductions in ulcer surface area, wound discharge, and slough, as well as the early appearance of granulation tissue. They also have potent antibacterial properties and offer significant reductions in wound culture positivity. Therefore, nanocrystalline silver dressings are a beneficial and superior alternative to normal saline dressings for managing lower limb ulcers.

Key words: Dressings, Lower limb ulcers, Nanocrystalline silver, Normal saline

INTRODUCTION

Ulcers of the lower limb are one of the most common issues encountered by surgeons. Dressings have a key role in the management of ulcers, and a variety of compositions and substances have been used in the literature for the management of lower limb ulcers. Proper cleansing is an important aspect of managing acute and chronic wounds to create a wound environment conducive to healing. Cleaning techniques vary among health-care professionals, organizations, and facilities and are frequently based on unique experiences and personal preferences.[1] Choosing the right wound dressing is a critical part of managing diabetic wounds. The dressing should be inexpensive, convenient, and non-allergenic, promote airflow, keep the wound moist, absorb excess exudate, provide insulation and protection, control odor, prevent contamination, and reduce the risk of infection.[2] There are numerous types of dressings on the market, including saline, hydrogels, hydrocolloids, foams, alginates, paraffin, and silver

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Corresponding Author: Dr. Arun Pandey, Department of General Surgery, Shri B M Patil Medical College Hospital and Research Centre, Vijayapura, Karnataka, India.

dressings. Normal saline dressings are economical but provides a moist environment only for a short duration. Hydrogel dressings hydrate and relieve pain in dry wounds with necrotic eschar. Other wound treatments that have been recommended include vacuum-assisted devices, cultured skin, and hyperbaric oxygen therapy.[3,4] On the other hand, silver dressings containing silver nitrate or silver sulfadiazine are rapidly inactivated by wound fluid, necessitating frequent replacement, and potentially excessive silver delivery to the wound. In a different case study Voigt *et al*., the effects of nanocrystalline silver on four patients with decubitus ulcers; one ulcer that had been present for 24 months was cured in 27 days, while another had been present for 2 weeks and was healed in 14 days. In every case where nanocrystalline silver was used, they showed a decrease in exudate fluid quantities. Literature reveals that nanocrystalline silver is inexpensive, improves wound healing, and can be used on all types of wounds.[5] In another single-center, open-label, and unblinded pilot trial done by Kirsner *et al*. in 2002 with 11 extended-care facility outpatients or residents with mixed etiology chronic wounds to investigate silver's effect on wound healing. Every wound had a history of at least 3 months, and there had been no shrinkage of the wound size in the 3 weeks before the research. After the 1st week, the dressings were changed every other day, and all patients received a nanocrystalline silver treatment. For fluid analysis and fluid collection, all used dressings were saved. In the first 2 days of treatment, it was found a decrease in matrix metalloproteinase activity in eight participants who completed the study. This demonstrated that the changed matrix metalloproteinase activity might persist if the nanocrystalline silver dressing is used consistently.[6] Poon and Burd investigated the silver's effect on keratinocytes and fibroblasts. The two experimental dressings were silver nitrate solution and silver nanocrystals. They showed that silver was poisonous to germs as well as skin cells such as keratinocytes, fibroblasts, and fibroblasts. They advised against using silver products in areas where keratinocytes are exposed and rapidly reproducing, such as donor sites, superficial partial thickness wounds, and applications involving undifferentiated cultured keratinocytes.[7] Therefore, the present study aimed to investigate the impact of nanocrystalline silver dressings in the lower limb ulcers and compare them to traditional normal saline dressings.

MATERIALS AND METHODS

This prospective comparative interventional study was conducted in BLDE DU, Shri BM Patil Medical College Hospital and Research Centre, Vijayapura, on 70 patients from January 2021 to October 2022.

Type of Study

This study was prospective interventional study.

Time Period

This study was 22 months.

Sample Size

The sample size was 70.

Sampling

After taking into account the continuity correction and the assumption that 66% of the reference population have the factor of interest, the study required 35 participants in each group (70 in total assuming equal group sizes) to achieve a 99% power for detecting a −0.52 difference in proportions between the test and reference groups at a two-sided $P = 0.01$ (test – reference group).[8]

Formula used

$$n = \frac{\left(z_\alpha + z_\beta\right)^2 2\,p * q}{MD^2}$$

Where Z= Z statistic at a level of significance
MD= Anticipated difference between two proportions
P=Common Proportion
q = 100-p

Statistical Analysis

The data obtained were entered in a Microsoft Excel sheet, and statistical analysis was performed using a Statistical Package for the Social Sciences. Results were presented as mean SD, counts, and percentages and diagrams. Normally distributed continuous variables between two groups were compared using the independent t-test. For not normally distributed variables, the Mann–Whitney U-test was used. Categorical variables between the two groups were compared using the Chi-square test. $P < 0.05$ was considered statistically significant. All statistical tests were performed in two-tailed.

Inclusion Criteria

Patients presented to general surgery OPD with lower limb ulcer of size <15 cm × 15 cm.

Exclusion Criteria

Patients who were immunologically compromised, are known to be allergic to silver-containing compounds and have malignant non-healing ulcers and burn patients are excluded from the study.

Methodology

A total of 70 patients, with 35 patients in each group, participated in a comparative interventional study. The

researchers conducted a detailed clinical examination and relevant investigations to record the initial wound area, presence/absence of discharge, slough, granulation tissue, and culture after debridement by measuring length x width (provided ulcer should be <15 cm × 15 cm). Once-daily dressings were administered to both groups, and the patients were followed up daily for 2 weeks. The outcome, or the area of the target ulcer, was measured using a transparent graph sheet and planimetry. The results were calculated using the Chi-square test.

The patients were divided into the following groups based on the results at the end of the study period: complete responders, who had complete healing of ulcer; partial responders, who had more than 50% wound healing; non-complete responders, who had <50% wound healing; and non-responders, who did not show any signs of wound healing.

RESULTS

A total of 70 patients with lower limb ulcers were included in the study and were divided into two groups on an alternate basis: the study group (Nanocrystalline group) and the control group (Normal saline group). The age distribution of patients was between 16 and 78 years of age, with more percentage of the patients belonging to 50–59 years followed by 40–49, 60–69, 20–29, and 70+ years of age groups in the study group. In the control group, more patients were 50–59 years, followed by 40–49, 60–69 and 30–39-, and 20–29-year age groups. In the present study, the incidence of wound discharge after 2 weeks of treatment was present in 4 (11.4%) patients and absent in 31 (88.6%) patients in the study group. In the control group, wound discharge after 2 weeks was present in 12 (34.3%) patients and absent in 23 (65.7%) patients. The results were statistically significant ($P = 0.0228$) [Figure 1].

In the present study, the incidence of granulation tissue was higher in the study group (Nanocrystalline silver group) after 2 weeks. Granulation tissue was present in 34 (97.1%) patients and absent in 1 (2.9%) patient in the study group. In the control group (Normal Saline group), granulation tissue was present in 27 (77.1%) patients and absent in 8 (22.9%) patients. The study group showed better results in the appearance of granulation tissue, which were statistically significant ($P = 0.0124$) [Table 1].

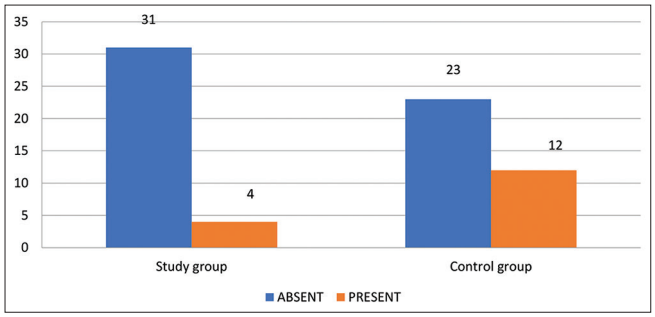

Figure 1: Wound discharge after 2 weeks

In the present study, the incidence of slough after 2 weeks was higher in the control group. In study group 2 (5.7%), patients' slough was present, and 33 (94.3%) patients' slough was absent. In the control group, 10 (28.6%) patients' slough was present, and 25 (71.4%) patients' slough was absent after 2 weeks of study. Hence, the study group shows a significant reduction in slough compared to normal saline ($P = 0.0112$) [Table 2].

In the present study, the incidence of mean reduction in ulcer surface area was seen more in the study group than in the control group. In the study group, the mean reduction in ulcer surface area is 54.63%; in the control group, the mean reduction in ulcer surface area is 27.09%. The results are statistically significant ($P = 0.0001$*) [Table 3].

After 2 weeks, 3 (8.5%) patients had culture-positive and 32 (91.5%) patients had culture-negative in the study group. In the control group, 10 (28.6%) patients had culture-positive and 25 (71.4%) patients had culture-negative. Hence, the study group is more efficiently inhibiting the growth of bacteria compared to the normal saline group ($P = 0.0314$). In the study group, 11 (31.4%) patients were complete responders, 6 (17.1%) patients were non-complete responders, 5 (14.3%) patients were non-responders, and 13 (37.1%) patients were partial responders. In the control group, 3 (8.6%) patients were complete responders, 7 (20%) patients were non-complete responders, 18 (51.4%) patients were non-responders, and 7 (20%) patients were partial responders. The results were statistically significant ($P = 0.0032$) [Figure 2].

DISCUSSION

Lower limb ulcers are one of the most common problems general surgeons encounter. Chronic pain and disability significantly hampers quality of life. Majority of diabetic patients underwent surgical treatment, the maximum being hand/toe amputations. Chronic diabetes increases the risk of developing foot ulcers.[9] Silver nanoparticles have greater antimicrobial properties. These particles provide higher surface area to volume ratios and less toxic to human cells.[10] It is a comparative interventional study, a total of 70 patients with lower limb ulcers between the age group of 16 and 80 participated in the study were randomly divided into two groups; the nanocrystalline group and the normal saline group. Parameters such as age, wound surface area, presence/absence of discharge, presence/

Table 1: Granulation tissue after 2 weeks

Granulation tissue -initial	Study group		Control group		Chi-square test	*P*-value
	No. of patients	Percentage	No. of patients	Percentage		
Absent	1	2.9	8	22.9		
Present	34	97.1	27	77.1		
Total	35	100.0	35	100.0	6.248	0.0124
						Statistically significant

Table 2: Slough after 2 weeks

Slough-after	Study group		Control group		Chi-square test	*P*-value
	No. of patients	Percentage	No. of patients	Percentage		
Absent	33	94.3	25	71.4		
Present	2	5.7	10	28.6		
Total	35	100.0	35	100.0	6.437	0.0112
						Statistically significant

Table 3: Comparison of reduction in ulcer surface area between study and control group

Reduction in ulcer surface area	Study group		Control group		Mann whitney U test	*P*-value
	Mean	SD	Mean	SD		
Reduction in ulcer surface area	54.63	30.235	27.09	26.764	308.500	*P*=0.0001*

*Statistically significant

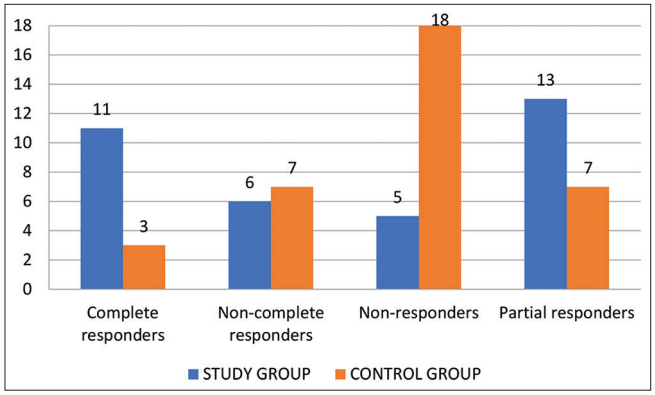

Figure 2: Study outcome

absence of slough, granulation tissue, and reduction in mean ulcer surface area were compared at zero and after 2 weeks of treatment.

In the present study, the incidence of lower limb ulcers was higher in males than in females. Study group had 29 (82.9%) males and 6 (17.1%) females, control group had 31 (88.6%) males and 4 (11.4%). Both groups' outcomes were comparable, and they were statistically insignificant. In a study by Gupta *et al.*, the study group's mean age was 54.47 years, compared to 59.93 years for the control group.[8] Both groups' distributions of age and sex were comparable and statistically insignificant. The outcomes and the present study were equivalent. After 2 weeks, the study group's discharge rate drastically decreased. In a study by Gupta *et al.*, both the study and control groups had purulent discharge. Even yet, there was a slow transition from purulent to serous discharge, and the study group experienced a quicker reduction in flow. These findings were statistically significant.[8] The results are comparable with the present study.

The study group showed better results in the early appearance of granulation tissue, which were statistically significant ($P = 0.0124$). Unlike the present study, Gupta *et al.* demonstrated the appearance of granulation tissue in the nanocrystalline and the normal saline groups was similar, with statistically insignificant results ($P = 0.283$).[8]

After 2 weeks, the study group showed a significant slough reduction compared to the normal saline group ($P = 0.0112$). Gupta *et al.* demonstrated a considerable reduction in slough in the nanocrystalline silver group compared to the normal saline group ($P = 0.045$). The results were comparable to the present study. In the present study, the incidence of mean reduction in ulcer surface area was seen more in the study group than in the control group. In the study group, the mean reduction in ulcer surface area is 54.63%; in the control group, the mean reduction in ulcer surface area is 27.09%. Hence, the study group shows a significant reduction in ulcer surface area compared to the normal saline group ($P = 0.0001$*). Gupta *et al.* conducted a similar study in which the mean initial ulcer size in the study group was 55.67 cm square and

54.93 cm square in the control group. The mean ulcer size in the study population was 9.23 cm square after 8 weeks, and 18.31 cm square in the control group.[8] The results were statistically significant and comparable to our study.

Initially, a higher incidence of negative culture was noted compared to a positive culture in both groups. However, there were more positive cultures in the study group. There were 15 (42.9%) patients with culture-positive and 20 (57.1%) patients with culture-negative in the study group. In the control group, 11 (31.4%) patients had culture-positive, and 24 (68.6%) had culture-negative. After 2 weeks, a higher incidence of negative culture was noted compared to a positive culture in both groups. However, there were more positive cultures in the control group than the study group, even after 2 weeks of treatment. There were 3 (8.5%) patients with culture-positive and 32 (91.5%) patients with culture-negative in the study group. In the control group, 10 (28.6%) patients had culture-positive, and 25 (71.4%) patients had culture-negative. Hence, the study group is more efficiently inhibiting the growth of bacteria compared to the normal saline group ($P = 0.0314$). Wright *et al*., Yin *et al*., and Voigt *et al*. conducted a similar study and attributed it to nanocrystalline silver's potent and rapid antibacterial activity.[5,11,12]

The incidence of complete and partial responders was higher in the study group than in the control group. However, the incidence of non-responders and non-complete responders was higher in the control group than in the study group. In the study group, 11 (31.4%) patients were complete responders, 6 (17.1%) patients were non-complete responders, 5 (14.3%) patients were non-responders, and 13 (37.1%) patients were partial responders. In the control group, 3 (8.6%) patients were complete responders, 7 (20%) patients were non-complete responders, 18 (51.4%) patients were non-responders, and 7 (20%) patients were partial responders. Hence, the study group responded more efficiently and effectively as compared to the control group, and the results were statistically significant ($P = 0.0032$).

Sharma *et al*. found a higher percentage of complete responders (84.6%) in a similar study, which could be attributed to the longer duration of treatment in their study (12 weeks); however, they also supported the fact that nanocrystalline silver ions accelerate wound healing.[13]

Greater antibacterial capabilities are provided by nanotechnology employing silver ions. Due to their smaller size and higher surface area to volume ratios, silver particles are less hazardous to human tissue cells.[10,14] Silver ions promote wound healing by accelerating fibroblast proliferation and differentiation into myofibroblasts. The rapid transformation of fibroblasts into myofibroblasts was seen, hence causing faster wound contraction in a study by Liu *et al*.[15] Nanocrystalline silver reduces excess matrix-metalloproteinase activity, hence proved to be ideal for dressings of chronic wounds, as per a study by Widgerow *et al*.[16] A study by Dutt *et al*. concluded that functionalized silver nanoparticles could be useful in creating a therapeutic agent for dressing infected chronic ulcers.[17]

In a study by Fong and Wood, he demonstrated that nanocrystalline silver is cheaper and limits infection, requiring frequent dressings, and hence promoting early healing of chronic ulcers.[18] In another trial done by Nherera *et al*., they found nanocrystalline silver dressings to be a cheaper and pocket-friendly silver delivery system, followed by silver-impregnated hydrofiber dressings.[19] Nanocrystalline silver promotes free oxygen radicals that aid in bacteriostatic action; Sondi and Salopek-Sondi, in another study, demonstrated the antibacterial properties of silver against *Escherichia coli*.[20-22] Thomas *et al*. revealed that acticoat silver dressing has the most potent antibacterial effect against *E. coli*, *Staphylococcus*, and yeast.[23] "Silver oxysalts" dressings improve wound healing by modulating oxidative stress in the wound environment and antimicrobial characteristics.[24] Metallic nanoparticles will be an innovative class of antimicrobials. Nanoparticles largely adhere the harmful organism to its surface and compromise its permeability leading to cell death. These particles also limit bacterial nutrition intake from the wound environment.[25-27] Beyond their traditional role as an antibacterial agent, nanoparticles are now being used to treat cancer and immunological illnesses.[28,29]

Study Limitations

The study's limitations were less sample size and short follow-up period.

CONCLUSION

Nanocrystalline silver dressings have resulted in a notable decrease in the surface area of ulcers, a rapid reduction of wound discharge, slough, and an early granulation tissue formation. Moreover, it exhibits potent antibacterial properties and significantly reduces wound culture positivity rate. Thus, using nanocrystalline silver dressings proves highly beneficial and effective compared to normal saline dressings in managing lower limb ulcers.

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