Original Research Article

Comparing the efficacy of nano crystalline silver dressing versus betadine dressing in management of diabetic foot ulcer

Bhavkeerat Singh*, Sudershan Kapoor, Arun Kumar Gupta

Department of Surgery, Sri Guru Ram Das Institute of Medical Sciences and Research, Vallah, Sri Amritsar, Punjab, India

Received: 25 March 2020
Revised: 09 April 2020
Accepted: 10 April 2020

*Correspondence:
Dr. Bhavkeerat Singh,
E-mail: drbhavkeerat@gmail.com

ABSTRACT

Background: The incidence of diabetes and its complications is rising as a result of the lifestyle changes. The foot is most frequent site for complication in patients with diabetes. Dressings have a vital part to play in the management of wounds. The ideal antiseptic is one that is lethal to all forms of bacteria, has no deleterious effect on healing tissues, delineates the operative areas, easily applied and has wide spectrum of activity and absence of acquired bacterial resistance. Nanotechnology makes it possible to expand the surface area of silver particles markedly to nanoscale. They expand the surface area of silver particles increasing their contact with bacteria.

Methods: In the proposed study, over a period of 18 months, 60 cases (30-30 in 2 groups) of diabetic foot ulcers were studied with respect to response (healing) to nano silver dressing and betadine dressing after dividing them randomly. Assessment was based on various parameters like size reduction, healthy granulation tissue, etc.

Results: It was seen that percentage reduction in size, was more in nano silver group as compared to betadine group. Wounds were managed successfully, early in nano silver group and wound healing was better in nano silver group as compared to betadine group. Also, nano silver was better antimicrobial.

Conclusions: The prospective study showed nano silver gel is safe and effective in wound management and gives better efficacy and faster response as compared to traditional betadine dressing.

Keywords: Diabetic foot ulcers, Nano silver gel, Wound management

INTRODUCTION

The ultimate goal for wound healing is a fast recovery with negligible scaring and best function. Wounds expose patient to various hazards like infection, tissue necrosis, disfigurement and scars. It is the surgeons’ task to minimize the adverse effects of injuries, remove or repair the damage structure and hasten the process of wound healing to restore the function. Poor glycemic control results in lessened inflammatory response, neovascularization and collagen synthesis therefore delaying healing. It is interaction of contributory causes which leads to the breakdown of the foot at risk.

There are 4 main causes for development of foot lesion in a diabetic.

Neuropathy

The commonest diabetic poly neuropathy is distal symmetrical neuropathy, affecting about 30% of all diabetic people.1,3 Vascular and metabolic factors are both implicated in the pathogenesis. Proposed hypotheses are chronic hyperglycemia, oxidative stress, neurotrophic factors, vascular factors.4
Peripheral vascular disease

Macro vascular disease like atherosclerosis, diffuse intimal fibrosis and micro vascular disease like arteriosclerosis, specific diabetic microangiopathy, diabetic fibrosis.5,6

Charcot foot

Bone and joint damage in the tarso metatarsal joints and mid-tarsal joints leads to two classical deformities.7

Infection

Infection of the plantar space accounts majority of diabetic foot infections. Majority start with infected ulcers on the plantar aspect of the foot and nail bed infections.

The Hippocratic teachings described clearly the use of antimicrobials such as wine and vinegar which were widely and successfully used to irrigate open and infected wounds before secondary closure at a later date.8 Over the past several decades a series of clinical trials have examined the effect of number of different agents viz. host factors, microbes and use of appropriate antibiotics affecting the healing of different types of wounds and recovery of the patients.

The irrigation of wounds with antibiotics/antiseptics containing solutions has significantly reduced wound infections particularly in contaminated or clean contaminated procedures antiseptic agents also may control bacterial load and prevent the development of infection but may also be toxic to fibroblasts and other viable cells.9 However, silver has only a very weak toxic potential and only rarely induces microbial resistance. In vitro studies have demonstrated the effectiveness of silver-based dressings against pathogenic bacteria.10 Thus, use of silver-releasing dressings in conjunction with debridement on wounds at risk of developing infection is beneficial.9,11 Nanotechnology has facilitated the production of very small size silver particles with increasingly large surface area to volume ratios, which imparts greater antimicrobial efficacy and most importantly lowers their toxicity to human tissue cell.12

The use of silver as a prophylactic and treatment for infection and other diseases dates back to about 1000 BC, when the ancient Greeks and the Romans used it as a disinfectant.9-11 Silver foil applied to surgical wounds were known to improve wound healing and reduce post operative infections, and silver pencils were used to remove warts and to debride ulcers.13,14

The potency of silver as an antimicrobial was found to be related to the amount and rate of free silver released onto the wound bed.15 The potency of silver as an antimicrobial was found to be related to the amount and rate of free silver released onto the wound bed.15

Silver has antiseptic, antimicrobial, anti-inflammatory properties and is a broad spectrum antibiotic.13,15 Silver is biologically active when it is in soluble form i.e., as Ag⁺ or Ag₀ clusters. Ag⁺ is the ionic form present in silver nitrate, silver sulfadiazine, or other ionic silver compounds. Ag₀ is the uncharged form of metallic silver present in nanocrystalline silver.16 Free silver cations have a potent antimicrobial effect which destroys microorganisms immediately by blocking the cellular respiration and disrupting the function of bacterial cell membranes. This occurs when silver cations bind to tissue proteins, causing structural changes in the bacterial cell membranes which in turn cause cell death. Silver cations also bind and denature the bacterial DNA and RNA, thus inhibiting cell replication.14,15

Wright et al examined early healing events and the efficacy of nanocrystalline silver on the levels of matrix metalloproteinase, cell apoptosis and healing in a porcine model of contaminated wounds and observed that nanocrystalline silver has a role in altering the inflammatory events in wounds and facilitate the early phase of wound healing.17

A comparative laboratory study reported that nanocrystalline silver dressings reduced the pathogenic bacterial count for *Staphylococcus aureus* and *Pseudomonas aeruginosa* below the limit of detection (less than 10 cfu/ml) by 24 hours. This high efficacy was maintained with higher concentrations of bacteria at 48 hours.18

A study of induced contact dermatitis in guinea pigs compared five daily applications to the affected area of one of the following: topical nanocrystalline silver cream, medium and high potency steroids, tacrolimus and pimecrolimus. The effect of nanocrystalline silver appeared to be more rapid.19

Hence, our objective in this study was to compare the wound healing outcome in diabetic foot ulcers between the conventionally used dressings i.e. betadine dressing and nano crystalline dressing.

METHODS

Cases of diabetic foot ulcers admitted in the in-patient department in Sri Guru Ram Das Institute of Medical Sciences and Research, Vallah, Sri Amritsar were considered in this study. Study was undertaken after the approval from the Hospital Ethics Committee. Prospective comparative study was done from December 2017 to June 2019. Informed written consent was taken from all the patients after explaining to them, the procedure and purpose of this study. Total of 60 cases were enrolled in study. Patients were randomly divided into two groups of 30 each. In first group, after cleaning wound with normal saline, nano silver crystalline gel was applied over the wound covered with paraffin mesh, while in the second group, betadine soaked gauze was
applied. There was follow up of 8 weeks and ulcer status was noted using visual assessment, thus analysing the response of ulcers to both dressings.

Patients were selected on the basis of inclusion and exclusion criteria.

**Inclusion criteria**

All the patients more than eighteen years, patients of both sexes, patients admitted in department of general surgery, medicine and orthopaedics, patients with diabetic foot ulcer conditions, ulcer size up to 10×10 cm were included.

**Exclusion criteria**

Patients less than 18 years, patients with significant co morbidities like liver cirrhosis etc., patients positive for HBsAg, HCV and HIV, patients on steroids, immunosuppressive agents, radiation, or chemotherapy were excluded.

**Procedure**

Patients were divided into 2 groups of 30 each. In first group, after cleaning wound with normal saline, nano silver crystalline gel was be applied over the wound covered with paraffin mesh, while in the second group, betadine-soaked gauze was applied. There was follow up of 8 weeks and ulcer status was noted using visual assessment, thus analysing the response of ulcers to both dressings.

Each patient received treatment with nano silver dressing after cleansing wound with normal saline in group A and conventional dressing without nano silver in group B.

Needful debridement was done when needed and sufficient quantities of antiseptic solution were applied to rinse the wound bed free of debris. The dressing was held in place with bandages wherever needed.

Examination of wound was done and status of wound noted on day of admission, then at the weeks 1, 2, 4 and 8 respectively while doing dressings.

Pus for culture and sensitivity (c/s) was sent on day 1 of admission. At these visits, complete physical examination, concomitant therapy, clinical examination of wound and assessment of adverse effects were carried out.

Laboratory test including Hb, CBC, HbA1c, blood sugar, renal function tests were carried out.

The complete microbial investigation including the organisms found in the lesions along with their susceptibility to different antibiotics was done at the baseline.

**Statistical analysis**

The study data was analysed to evaluate the effect of nano crystalline silver dressing over betadine dressing. SPSS software and Microsoft Excel software are used in this analysis. Chi-square test is used to evaluate the results and p<0.05 is considered to be significant.

**RESULTS**

The study comprising of 60 patients prospectively randomized into two groups having 30 patients in each group (group A and B).

In first group, after cleaning the wound with normal saline, nano silver crystalline gel (group A) was applied over the wound covered with paraffin mesh, while in the second group, betadine (group B) soaked gauze was applied. Maximum follow up period of 8 weeks was undertaken and ulcer status was noted using visual assessment, thus analysing the response of ulcers to both dressings.

Attempts were made to include patients having similar type of wounds in both groups. The assessment of healing of wound was based on various parameters like reduction in size, discharge, edge and margin status, appearance of granulation tissue of the wounds.

As depicted in Table 1, patients of different age groups were studied. Maximum number of patients being in age group of 40-50 overall (in group A) and second being the age group of more than 60 years (in group B). Mean age in group A was 53.80±9.81 years. Mean age in group B was 58.20±10.70 years.

Table 1: Age distribution.

<table>
<thead>
<tr>
<th>Age group (in years)</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-50</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>51-60</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>&gt;60</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

As per Table 2, it was noted that sex distribution did not carry much of significance. The Table shows that in group A, 60% of patients were males and 40% patients were females whereas group B also encompassed 66.67% males and 33.33% females.

In Table 3, it was seen that in group A, 14 out of 30 patients had HbA1c >10 (poor glycaemic control), while in group B, 12 out of 30 patients had HbA1c >10.

Table 4, showed that in group A, initial wound size was 7.01±4.40 cms and in group B, initial wound size was 8.24±5.13 cms (p<0.324). During the study at 4 weeks, in group A, final wound size at 4 weeks was 1.12±1.04 cms...
and in group B, final wound size was 2.84±4.16 cms (p=0.042). Wound size is comparably less in group A than in group B at 4 weeks follow-up (p<0.05).

Table 2: Sex distribution.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N %</td>
<td>N %</td>
</tr>
<tr>
<td>Male</td>
<td>18 60.00</td>
<td>20 66.67</td>
</tr>
<tr>
<td>Female</td>
<td>12 40.00</td>
<td>10 33.33</td>
</tr>
<tr>
<td>Total</td>
<td>30 100.00</td>
<td>30 100.00</td>
</tr>
</tbody>
</table>

Table 3: Co-morbidities.

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N %</td>
<td>N %</td>
</tr>
<tr>
<td>&lt;6</td>
<td>0 0.00</td>
<td>1 3.33</td>
</tr>
<tr>
<td>6-10</td>
<td>16 53.33</td>
<td>17 56.67</td>
</tr>
<tr>
<td>&gt;10</td>
<td>14 46.67</td>
<td>12 40.00</td>
</tr>
<tr>
<td>Total</td>
<td>30 100.00</td>
<td>30 100.00</td>
</tr>
<tr>
<td>Mean HbA1c</td>
<td>9.87±2.09</td>
<td>9.95±3.05</td>
</tr>
</tbody>
</table>

P value: 0.878.

Table 4: Wound size.

<table>
<thead>
<tr>
<th>Wound size in cms at different time period</th>
<th>Group A</th>
<th>Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Initial</td>
<td>7.01</td>
<td>4.40</td>
<td>8.24</td>
</tr>
<tr>
<td>1st week</td>
<td>5.29</td>
<td>3.93</td>
<td>6.93</td>
</tr>
<tr>
<td>2nd week</td>
<td>2.76</td>
<td>2.05</td>
<td>4.01</td>
</tr>
<tr>
<td>4th week</td>
<td>1.12</td>
<td>1.04</td>
<td>2.84</td>
</tr>
<tr>
<td>8th week</td>
<td>-</td>
<td>-</td>
<td>0.32</td>
</tr>
<tr>
<td>Difference (initial - 4th week)</td>
<td>5.89±0.92</td>
<td>5.40±0.98</td>
<td>0.042</td>
</tr>
</tbody>
</table>

As shown in Table 5, we observed that most of the ulcers healed completely with nano silver gel and betadine dressings only, while some of the ulcers were managed with grafting, flap and amputation. Till 4th week, in group A, 18 out of total 30 patients healed entirely by applying nano silver gel, while in group B,10 wounds were healed by betadine dressing. One patient of each group had undergone amputation by 4th week. 2 patients in group A underwent grafting, while in group B, 10 patients had to undergo grafting. Whereas one patient in group A was managed with primary suturing and one patient with flap. Wounds in 7 patients in group A and 9 patients in group B were not healed by dressings by the time of 4 weeks.

Table 5: Wound healing status at fourth week.

<table>
<thead>
<tr>
<th>Status of wound at 4th week</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N %</td>
<td>N %</td>
</tr>
<tr>
<td>Amputate</td>
<td>1 3.33</td>
<td>1 3.33</td>
</tr>
<tr>
<td>Grafting</td>
<td>2 6.67</td>
<td>10 33.33</td>
</tr>
<tr>
<td>Healed</td>
<td>18 60.00</td>
<td>10 33.33</td>
</tr>
<tr>
<td>Flap</td>
<td>1 3.33</td>
<td>0 0.00</td>
</tr>
<tr>
<td>Primary suturing</td>
<td>1 3.33</td>
<td>0 0.00</td>
</tr>
<tr>
<td>Not healed</td>
<td>7 23.33</td>
<td>9 30.00</td>
</tr>
<tr>
<td>Total</td>
<td>30 100.00</td>
<td>30 100.00</td>
</tr>
</tbody>
</table>

Figure 1, depicts how various wounds in group A and group B were managed to give the final result.

As shown in Table 6, by 4 weeks time, no patient in group A had pale granulation. In group B, 16.66% patients had pale granulation. 26.67% patients in group A had pink granulation while in group B, 13.33% patients had pink granulation (p=0.042). Granulation tissue was comparably better in group A than in group B (p<0.05).
As per Table 9, no patient in group A had wound discharge at the end of four weeks while in group B, 16.66% patients still had wound discharge (p=0.042).

**DISCUSSION**

Nanocrystalline silver dressings should be used selectively for infected wounds, particularly in diabetics or patients with peripheral arterial occlusion disease in which systemic antibiotics often do not reach peripheral infection.

The effectiveness of a nanocrystalline dressing should be evaluated in weeks. Extension of use beyond this time period should be based on expert clinical judgement.

Wounds with moderate to high levels of exudate may require a secondary absorbent dressing, which should be changed on a regular basis as required.

A number of studies have found that silver dressings are associated with factors that may be beneficial in terms of cost effectiveness, e.g. reduced time to wound healing, shorter hospital stays, reduced dressing change frequency, reduced need for pain medication during dressing change, fewer MRSA bacteremia’s resulting from MRSA-infected wounds.20-26

Mendoza et al studied a direct co-relation between old age and poor wound healing outcomes such as dehiscence.27 Holt et al studied that, in comparison to healthy human volunteers, there was a significant delay of 1.9 days in the epithelisation of superficial skin defects in those older than 70 years of age.28 In this study different patients of different age groups were studied in both groups. In group A, the mean age was 53.80±9.81 years while in group B mean age was 58.20±10.70 years, so age distribution was comparable in both the groups. Age distribution did not carry much of inference in this study.

A study conducted by Kautzky-Willer et al, described that men develop diabetic foot syndrome at earlier age as compared to females. Also, one of the positive predictors for a higher risk of foot ulceration was male sex. 29 In this study also, it was the male gender that was suffering more from diabetic foot. Sex distribution did not carry much of inference in our study, as sex distribution was comparable in both the groups, comprising of 60% male patients and 40% female patients in group A and 66.6% male patients and 33.33% female patients in group B.

The study conducted by Heughan et al, concluded that patients having anaemia had slower wound healing rate as compared to healthy individuals.30 In our study, though majority of patients had anaemia, as a co-morbidity, the co-morbid condition was equally distributed in both the groups and no bias in study was there due to this condition, effecting wound healing.
A study by Xiang et al concluded that a reasonable HbA1c, ranging between 7.0 and 8.0 during treatment could facilitate ulcer healing without increase of mortality in patients with diabetic foot ulcers, especially for those with better glycemic control at admission. In this study, many patients had poor glycemic control as co-morbidity. In group A, 14 patients were having poor glycemic control whereas in group B, 12 patients had poor glycemic control. As the co-morbid condition being equally distributed in both the groups did not carry much of inference in study.

In a study conducted by Paola et al on 218 patients suffering from chronic diabetic foot ulcer, 110 patients were treated with silver solution and 108 with povidone solution. The mean healing time was 45±14 days with silver solution and 58±20 days with betadine group. In our study, at the end of 4 weeks the mean reduction in size in group A was 5.89±0.98 cms whereas in group B, the mean reduction in size was 5.40±0.98 cms (p<0.042) concluding that mean reduction in wound size was more in group A as compared to group B.

Lee et al investigated the effect of silver nanoparticles in dermal contraction and epidermal re-epithelialization during wound healing and suggested that silver nanoparticles could increase the rate of wound closure. In this study patients treated with nano silver gel showed early granulation with less eschar formation when compared to conventional dressing, betadine. During the average follow up period of 4 weeks, excluding the healed cases, 26.67% patients had healthy granulation tissue in group A, while in group B 16.66% of the patients had healthy granulation tissue (p<0.05). It concluded that healthy granulation formed earlier in patients treated with nano-silver dressing group as compared to betadine dressing group.

A study conducted by Versloot et al showed that nanocrystalline silver dressing had superior healing rates (89%), as compared with silver sulfadiazine dressings (68%). In our study, in group A percentage reduction in wound size was 84.2% at fourth week whereas in group B, percentage reduction in size was 65.5% at fourth week (p value 0.042) concluding that percentage reduction in size was more with nano silver gel as compared to betadine.

In a study conducted by Fong et al, the organism was inoculated onto each of the dressing, incubated for 30 minutes then washed with a recovery solution which then was cultured for organism survival rate. Out of nanocrystalline silver, silver nitrate solution, silver sulfadiazine cream and mafenide acetate, against 5 clinically relevant bacteria, nanocrystalline silver was found to be more rapid in the delivery of silver cations and achieved a faster reduction of bacteria than the other experimental dressings. Nanocrystalline silver killed bacteria faster. A study conducted by Ansari et al compared silver nanoparticles with amoxicillin and metronidazole, both commonly used topical antibiotics. Wounds treated with silver nanoparticles completely healed in 25.2±0.72 days after injury, whereas those treated with antibiotics required 28.6±1.02 days (p<0.01). This finding suggests that silver particles are more effective anti-bacterial agents. In our study, at an average 4 weeks follow up, no patient in group A had pus discharge while 16.67% of the patients of group B still had pale coloured discharge, concluding that there was more reduction in wound discharge at fourth week in group A as compared to group.

CONCLUSION

Nano silver gel is safe and effective in wound management and gives better efficacy and faster response as compared to traditional iodine and other topical antiseptics. It is less painful during cleaning and debridement procedures. The result of this study therefore appears to show more favourable results for nano silver gel group than for conventional dressing. Hence nano crystalline silver dressing is preferred over betadine in diabetic foot ulcers.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

Williams NS, Christopher JK, editors. 24th Ed. London: Bulstrove (Publishers); 2004; 110-118.