

Original Research Article

A comparative study on the wound healing effectiveness of with normal saline and ionized nano-crystalline silver dressing among chronic diabetic foot ulcer patients

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ABSTRACT

Background: Leg ulcers are debilitating and painful which greatly reducing diabetic patient's quality of life. A prospective cohort study was done to evaluate the effectiveness of wound healing of ionized nano-crystalline silver and normal saline was assessed.

Methods: Diabetic patients presented with foot/leg ulcer were divided into 2 groups of 28 in each group. In group 1 patients, sterile cotton gauze impregnated with normal saline was used. Group 2 patients were dressed with sterile cotton gauze impregnated with ionized nano-crystalline silver. Patients were observed for three weeks or until discharge. The rate of wound healing was assessed in three weeks with serial photographs and measurement of ulcers.

Results: Total 60 patients were included in the study. In the group 1, thirty-three patients whose ulcer was dressed with normal saline, the healing rate was 1.2 mm/day with an average value of 0.4 mm/day. The granulation tissue developed was dull red and unhealthy. While twenty-seven patients in group 2, whose ulcer dressed with nano-crystalline silver healing rate was found maximum of 1.5 mm/day with an average value of 0.6 mm/day. The granulation tissue developed was bright red and healthy. The area reduction of wound was significantly different between the groups and maximum was found on 15th day ($p=0.001$).

Conclusions: Wound dressing with ionized nano-crystalline silver was better than normal saline. This suggest the potential use of nano- silver based dressing in diabetic leg and foot ulcer patients.

Keywords: Diabetic foot ulcer, Neuropathy, Nano-crystalline silver, Normal saline

INTRODUCTION

Diabetes mellitus (DM) affects 8.3% of population or 382 million of people which will increase the risk of foot ulcers. The diabetic foot infection increases the rate of hospital readmissions, amputations and mortality.¹ Leg ulcers are debilitating and painful, greatly reducing patient's quality of life.² Diabetic foot ulcer by definition is, infection, ulceration or destruction of deep tissues associated with neurological abnormalities and various

degrees of peripheral vascular diseases in the lower limb. Diabetic foot ulcers are the consequence of multiple factors including peripheral neuropathy, decreased blood supply, high plantar pressures leading to significant risk for morbidity, limb loss and mortality.³ Diabetic foot infections are a frequent clinical problem and if it is not properly managed. In patients with diabetic foot ulcer, glucose control is the most important metabolic factor. But many patients needlessly undergo amputations because of improper diagnostic and therapeutic approaches.⁴ In

addition to systemic antibiotics and surgical intervention, wound care is considered to be an important component of diabetic foot ulcer management. Silver ion (Ag⁺), as a broad antimicrobial spectrum has been used for wound treatment since 69 B.C.⁵⁻⁸ Studies have not yet been established the effectiveness of normal saline dressing and ionized nano-crystalline silver in healing the diabetic foot ulcer. Therefore, this study was aimed to compare effectiveness of standard normal saline dressing and ionized nano-crystalline silver dressing.

METHODS

Study design and sampling

Prospective cohort study was designed among diabetic patients presented with leg and foot ulcers in the Department of General Surgery, GMC Palakkad, Kerala, India during one-year period from February 2019 to January 2020. All patients (age ranging from 21 to 80 years) admitted with leg and foot ulcers, who gave informed consent to participate were included in the study. Patients suffering from immunodeficiency, malignancy or under treatment with steroids were excluded from the study. The study was conducted after getting clearance from Institutional research committee and Institutional ethics committee.

Sample size

All the diabetic patients who presented with leg and foot ulcers during the period of the study with the inclusion criteria were included in the study. Using the wound area reduction in two groups on 1st day obtained in this study, at 5% of significant level and power of 80%, the minimum sample size was calculated as $30 (15/\text{group}) [(r+1/r) (SD)^2 (Z\beta+Z1-\alpha/2)^2/d^2]$. The subjects were randomly assigned into groups.

Study procedure

All patients underwent a detailed history and clinical examination. Systemic antibiotics were given in culture positive cases. Complete control of diabetes was done. Blood sugar was monitored and maintained the euglycemic state using insulin and oral hypoglycemic agents during the therapy. After removing slough from the wound, dressing was given. In twenty-seven patients, ionized nano-crystalline silver dressing was given. In another thirty-three cases, normal saline was used for wound dressing. Clinical assessment was done with serial photography of the ulcer. Area of the ulcer, development of granulation tissue and size of the ulcer were measured over 2 days interval. Each patient was studied for three weeks or until discharge of the patient.

Statistical analysis

Data were analyzed using Statistical package for social sciences (SPSS) software (version 16, IBM, US). Values

were expressed as mean with SD. Unpaired t test was used to find the significant difference between mean values and Fischer's exact test was used for gender comparison between the two groups. P<0.05 was considered significant.

RESULTS

Total sixty diabetic patients were included in the study. The demographic data of the patients were given in Table 1. No statistically significant difference could observe among any of the demographic details between the groups. All the patients were followed up until the completion of the study. No adverse effect or incident was observed during the period of the study.

Table 1: Demographic data and clinical characteristics of the study participants.

Demographic data and clinical characteristics	Groups		P value
	Ionized nano-crystalline silver dressing (n=27)	Normal saline (n=33)	
Age (years)	58.4±9.2	58.0±11.3	0.8828
Gender	Male 24 Female 3	Male 28 Female 5	0.4738*
Duration of diabetes (years)	12.2±7.3	14.0±10.9	0.4662
Serum glucose (mg/dl)	309.8±49.7	280.1±70.6	0.0743
HbA1C (%)	7.5±0.7	7.2±0.7	0.1040
Initial ulcer width length (mm)	32.5±20 81.6±41.3	29.1±20.2 71.0±24.9	0.5028 0.2245

*Fisher's exact test

Thirty-three patients were included in the group 1 whose ulcer was dressed with normal saline. Twenty-seven patients included in the group 2, whose ulcer were dressed with ionized nano-crystalline silver. The rate of wound healing and observation of the granular tissue were given in Table 2. Reduction of both wound length or width was evidenced in the ionized nano silver dressed group with the normal saline dressed group. Reduction width of wound on 15th day was found to be almost double in the ionized nano silver dressed group when compared to the normal saline group (p=0.001). The mean areas of reduction of wound on 15th day in the saline and ionized nano silver dressings were 21.79 and 41.19, respectively. The areas of reduction of wound on the 1st day of dressing were 1.46 and 2.82, respectively in the normal saline and ionized nano crystalline silver dressed groups. All the parameters were found statistically significant between the groups (p<0.01). The observation of the granulation tissue developed was given in Table 3.

Table 2: Effect of nano-crystalline silver and normal Saline dressing on diabetic foot ulcer.

Observation	Group	N	Mean±SD	P value
Reduction of length on 15 th day (mm)	Normal saline	33	6.33±2.71	0.001
	Nano crystalline silver	27	16.07±14.61	
Reduction of width on 15 days (mm)	Normal saline	32	3.44±2.50	0.001
	Nano crystalline silver	27	7.15±4.47	
Reduction of length on 1 st day (mm)	Normal saline	33	0.42±0.18	0.004
	Nano crystalline silver	27	1.06±0.99	
Area of reduction on 15 th day (mm ²)	Normal saline	33	21.79±9.74	0.001
	Nano crystalline silver	27	41.19±20.95	
Area of reduction 1 st day (mm ²)	Normal saline	33	1.46±0.69	0.001
	Nano crystalline silver	27	2.82±1.36	

Table 3: Effect of nano-crystalline silver and normal saline on granulation tissue.

Groups	Material used for ulcer dressing	Maximum and average healing rate/day (mm)	Granulation tissue developed
1 (n=33)	Normal saline	1.2, average: 0.4 mm	Dull red and unhealthy
2 (n=27)	Nano crystalline silver	1.5, average: 0.6 mm	Bright red and healthy

The healing rate was found maximum of 1.5 mm/day with an average value of 0.6 mm/day in the silver dressed group. In the group 1 patients where the ulcer was dressed with normal saline; the healing rate was found 1.2 mm/day with an average value of 0.4 mm/day. The dull red and unhealthy observation was found in the normal saline treated group while in the ionized nano crystalline silver treated group, the granulation tissue was bright red and healthy. The percent reduction of ulcer with ionized nano crystalline silver was 2.78% per day and with normal saline dressings is 1.45% per day, which was significant (<0.001).

DISCUSSION

Results of this study found that wound dressing with ionized nano-crystalline silver showed a healing rate of maximum of 1.5 mm/day and average healing rate of 0.6 mm/day with bright red and healthy granulation tissue. Ulcer dressed with normal saline showed a maximum healing rate of 1.2 mm/day and average healing rate of 0.4 mm/day and the granulation tissue developed was dull red and unhealthy. Silver has efficacy against wide spectrum of bacteria, virus and fungal infections.⁹ Silver-based compounds have been using in wound care since early 1970. Among them, silver nano compounds attracted recently as silver nano particles may enter into the cell via pinocytosis and endocytosis. Entry into the cell is followed by damage to deoxyribonucleic acid (DNA) and bacterial proteins that eventually resulting in bacterial death.¹⁰ One parts per million (ppm) silver is sufficient to achieve bactericidal action. Nano crystalline technology appears to give the highest, sustained release of silver to a wound without clear risk of toxicity.¹¹ Silver nano particles can release Ag⁺ ions at a greater rate than bulk silver, by virtue of their large surface area.¹² Use of a newer, relatively nontoxic antiseptic (example: silver dressings) is preferable to use of topical antibiotics, especially agents that are available for systemic use was concluded in previous study.¹³ An ionized nano-crystalline silver dressing was evaluated through an uncontrolled, prospective study of a case series of 29 patients with a variety of chronic non-healing wounds. The results showed a marked clinical improvement for the majority of wounds treated with the dressing.¹⁴ Previous study found that the use of silver foam dressings resulted in a greater reduction in wound size and more effective control of leakage and odor than did use of non-silver dressings.¹⁵ Another study concluded that infected diabetic foot ulcer could benefit from the antibacterial effectiveness of silver phosphate cellulose fibers.¹⁶ Our results was also consistent to those previous studies.

In DM, there is imbalance between matrix degrading enzymes, matrix metalloproteases (MMP), their tissue inhibitors, inhibitor MMP. Loss of collagen which is associated with DM can be due to decreased levels of its synthesis, enhanced metabolism or a combination of both. Non healing of diabetic foot ulcer display elevated MMP activity, with 30 to 60 fold increase in MMP 2 and MMP 9.¹¹ Dysregulated cellular function also play a part, such as T-cell immunity, leukocyte chemotaxis, phagocytosis, and bactericidal capacity.¹⁷ Increased T-lymphocyte apoptosis which inhibit healing, has been observed in patients with DM. In DM, the accumulation of glycation end products causes the up regulation of pro-inflammatory cytokines, interleukin-1 and tumor necrosis factor- alpha.¹⁸ There is increased risk of infection and poor wound healing due to decreased cell and growth factor response, diminished peripheral blood flow and decreased local angiogenesis. In hyperglycemia, endothelial dysfunction leads a decrease of vasodilators and increase of plasma thromboxane-A2 levels. The result is vasoconstriction and plasma

hypercoagulation in peripheral arteries leading to ischemia and increased risk of ulceration. Patient with infected diabetic foot ulcer should be prescribed a targeted antibiotic regimen based on wound culture results. Aggressive antibiotic treatment is essential. Wounds are commonly infected with Pseudomonas and Staphylococcus. Ischemia complicates matter further by reducing defense mechanisms.

Limitations

The major limitations of the study include the small sample size, short duration of the study. Hence, further detailed study with more sample size is warranted.

CONCLUSION

The study concluded that wound dressing with ionized nano-crystalline silver is better than wound dressing with normal saline in diabetic leg and foot ulcer patients. This emphasizes the significance of using nano-crystalline silver, a cost-effective agent as an early intervention in the management of diabetic foot ulcer along with systemic antibiotics to reduce the rate of amputations.

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