Section: Surgery

Research

EFFICACY OF TOPICAL HEPARIN ON DIABETIC ULCER-PROSPECTIVE STUDY

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Abstract

Background: To evaluate the efficacy of topical heparin in the treatment of Grade 1and Grade 2 diabetic ulcers. **Materials and Methods:** A prospective interventional study was conducted with 80 patients alternatively assigned to two groups, i.e., 40 patients to topical heparin solution dressing group (Cases) and 40 patients to conventional dressing group (10% povidone iodine). **Result:** The reduction in the surface area of wound with time was more significant in Cases as compared to Controls. By day 14 , a significantly more number of Cases developed a healthy granulation tissue as compared to the Controls ($p< 0.005$).By 14 days, serous wound discharge was seen in 92.5% of case group and 70% in control group ($p< 0.001$. The mean duration of hospital stay was significantly shorter for Cases as compared to Controls (21.3 days ± 6.2 days vs 26.7 days ± 6.4 days, $p< 0.001$). **Conclusion:** Topical heparin dressing can be considered as a superior option in the management of diabetic ulcers. Nevertheless, we advocate further studies with a larger sample size to substantiate the findings we made.

INTRODUCTION

Diabetic foot ulcers have many pathogenic mechanisms, the most common etiology being peripheral sensory neuropathy, deformity, high plantar pressures, and peripheral arterial disease. Hyperglycaemia can decrease fibrinolytic activity, which increases blood viscosity and induces a high coagulation state in people with diabetes mellitus. The high coagulation state can damage vessel walls and lead to vascular dysfunction, coagulation- anticoagulation disorders. This high coagulation state contributes to the slow healing of diabetic foot ulcer.[1]

Wound healing in itself is a complex process. The complications of diabetes, like poor vascularity and uncontrolled infection, further increase its complexity. Diabetic foot ulcers are a significant cause of hospital admission and frequent cause of amputation resulting in economic loss and decreased quality of health.[2] Treating diabetic ulcers are challenging to surgeons as they contribute to morbidity, expenditure due to prolonged use of antibiotics and prolonged hospital stay.[3,4]

The standard management of diabetic ulcers includes debridement, control of infection, glycemic control and local dressings. Newer modalities like off-loading technique, local phenytoin sodium application, use of growth factors, laser therapy have been tried with modest results.

Heparin and related substances are glycosaminoglycans that exist naturally inside the cell and in the extracellular matrix. They act by binding selectively to varieties of proteins and pathogens and are important to many disease processes.[5,6] Their mechanism of action to be as follows:

1. They have beneficial effects on local tissue microcirculation and oxygenation through the inhibition of thrombin generation and increase in plasma fibrin gel porosity, which may promote vascular perfusion in the ischaemic foot significantly and lead to improvements in its blood supply.[7]
2. They can promote healing of chronic ulcers by stimulating production of basic fibroblast growth factor and transforming growth factor- beta.[8]
3. Laboratory work has also shown that they have positive effects in vitro, including promotion of the synthesis of heparin sulphate in endothelial cell culture,[9] and the proliferation of fibroblasts obtained from diabetic ulcer.[10]
4. Heparin can promote neo vascularisation in ischaemic limbs by improving the structure and number of capillaries.[11,12]
5. Heparin promotes migration of capillary endothelial cell and produces angiogenesis and thus formation of healthy granulation tissue.[13,14,15]

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6. It also reduces bacterial translocation and necessity for antibiotics is minimized.[16]
7. Heparin also enhances Type 1 collagen synthesis and hence the stable granulation tissue causes better healing.[17,18]

All these properties mean that heparin and related substances might act as a scaffold to enhance the activity of growth factors and reduce the inflammatory response in the ulcer bed.[1]

In this prospective study, we are comparing a novel method of using topical heparin solution in the management of diabetic foot ulcer grade I and II with conventional wound management using a 10 % povidone-iodine solution. The outcome of diabetic ulcer is compared between the two groups in terms of the wound area, granulation tissue, wound discharge, length of hospital stay and culture sensitivity.

Aims and Objectives

To evaluate the efficacy of topical heparin in the treatment of grade 1and grade 2 diabetic ulcers in the form of analyzing and comparing.

1. Wound area
2. Granulation tissue
3. Wound discharge
4. Duration of hospital stay.
5. Culture sensitivity

MATERIALS AND METHODS

Source of Data

This study was carried out in the Department of General Surgery, Shri B.M Patil Medical College, Hospital and Research centre, Vijayapura.

Study Period: From November 2018 to June 2020.

Study Design

Prospective, comparative study of efficacy of topical heparin solution dressing versus conventional dressing with 10% povidone- iodine solution in wound healing of grade I,II diabetic ulcer.

Study Sample

Total of 80 patients with 40 in each group i.e., 40 patients in study group and 40 patients in control group, patients were allotted to each group by alternate number randomisation.

Approval

Study was approved by the Institutional Medical Ethics Committee and written informed consent was obtained from all patients participating in the study.

Study Population

Patients with diabetic ulcers of Wagner's grade 1 and 2 during the study period were diagnosed on the basis of thorough clinical examination, appropriate laboratory and radiological investigations. They were included in the study based on the inclusion and exclusion criteria. A Proforma was used to collect all the relevant data from the patients. Detailed history was taken; thorough clinical examination and investigations were performed on all the patients included in the study. All the cases were followed up to discharge and subsequently for a follow up till wound healing.Data was entered on master chart for analysis. It was analyzed by using student t- test.

Inclusion Criteria

All the patients presenting with grade 1 and grade 2 diabetic ulcers of lower limb admitted in the Dept of Surgery, Shri B.M Patil Medical College, Hospital and Research centre, Vijayapura.

Exclusion Criteria

- Wagner's classification of diabetic ulcer grade 3 and above.
- With low platelet count or altered APTT/INR/sepsis
- Allergy to heparin
- Albumin <2gm/dl of blood, Hb<10.
- Patient with personal or familial history of bleeding disorders.
- Biopsy proven malignant ulcer.
- Patients with peripheral vascular disease diagnosed by Doppler study.
- Patients with multiple ulcers and size more than 10cm.

Statistical Analysis

- All characteristics were summarised descriptively. For continuous variables, the summary statistics of N, mean, standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and data was analyzed by Chi square test for association, comparison of means using t test, ANOVA and diagrammatic presentation.
- Method of Preparation of Heparin Solution for Topical Use
- Unfractioned heparin available in 5ml vials of 5000IU/ml strength was used. One vial was mixed with 100ml ml of normal saline and stirred to make heparinized sodium solution fit for topical application. The medication was applied to the ulcer drop by drop with 10ml syringe, once daily.
- Clotting time was done during the course of heparin treatment to monitor the dose of heparin. APTT and INR were done every 7 days. This was done to look into the systemic absorption of topically applied and its effects on bleeding profile of patient
- From infected wounds swabs were taken for culture and sensitivity, to monitor infection status of the wound.
- Initially broad-spectrum antibiotics started and later on antibiotic usage changed according to culture/sensitivity.

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- Doppler study of the affected limb to rule out the peripheral vascular disease.
- Patients were thoroughly examined and ulcer size (length, breath, depth) was measured.
- Every week the ulcer area was calculated by placing sterile gauze over the ulcer and two maximal perpendicular diameters were taken and multiplied.
- The wound area in cm2 and healing status of wound in terms of presence of granulation tissue, presence of discharge, duration of hospital stay, culture sensitivity was compared between two groups.
- End point of the study includes presence of healthy granulation tissue, culture negative wound and wound ready for grafting/ secondary suturing.

RESULTS

The mean age of patients in the case group was 57.1 years while it was 54.0 years in the control group. The mean age of the case group was not statistically different from that of the control group.

The sex distribution among cases and controls. Males predominated both the groups. The male: female ratio in the cases group was 5.7:1 whereas it was 3: 1 in the control group. The difference in sex distribution among cases and controls was not statistically significant.

[Table 1] show the reduction in mean surface area of ulcer between Cases and Controls at the end of 1 week, 2 weeks, 3 weeks and 4 weeks. The reduction in surface area at the end of each week is statistically significant in both Cases as well as Controls but the percentage of reduction is more in Cases as compared to Controls.

[Table 2] show the growth of healthy granulation tissue in Cases and Controls from day 0 to day 28. By day 7, 50% of Cases had developed a healthy granulation tissue which was significantly more than that developed in Controls (p <0.001). By day 14, 92.5 % Cases had a healthy granulation tissue as compared to 67.5% Controls who had developed a healthy granulation tissue. This difference was statistically significant (p< 0.005).

[Table 3] shows the serous wound discharge between Cases and Controls at the end of each week. By 7 days, serous discharge was seen in a greater number of patients in Case group as compared to Control group (50 % vs 25 %). By 14 days also, serous discharge was seen in a greater number of patients in Cases group as compared to Control group (92.5 % vs 70.0 %, p< 0.010).

[Table 4] shows the culture of Cases and Controls. There was significant difference among the two groups with regards to the distribution of microorganisms.

[Table 5] show the comparison of mean duration of hospital stay between Cases and Controls. The mean duration of hospital stay was significantly shorter for Cases as compared to Controls (p< 0.001).

Table 1: Reduction in mean Surface Area of Ulcer between Cases and Controls

Groups	Reduction in Surface Area of Ulcer (cm2)			
	Day 0 to Day 7	p value	Day 0 to Day 14	p value
Case	4%	<0.001*	10%	<0.001*
Control	3%	<0.001*	6%	<0.001*

Note: * significant at 5% level of significance (p<0.05)

Table 2: Healthy Granulation Tissue between Cases and Controls

Healthy Granulation Tissue	Case		Control		p value
	N	%	N	%	
0 DAYS	0	0.0%	0	0.0%	-
BY 7 DAYS	20	50.0%	11	27.5%	0.041*
BY 14 DAYS	37	92.5%	27	67.5%	0.005*
BY 21 DAYS	40	100.0%	40	100.0%	-
BY 28DAYS	40	100.0%	40	100.0%	-

Note: * significant at 5% level of significance (p<0.05)

Table 3: Wound Discharge between Cases and Controls

Serous Discharge	Case		Control		p value
	N	%	N	%	
BY 7 DAYS	20	50.0%	10	25.0%	0.048*
BY 14 DAYS	37	92.5%	28	70.0%	0.010*
BY 21 DAYS	40	100.0%	40	100.0%	-
BY 28DAYS	40	100.0%	40	100.0%	-

Note: * significant at 5% level of significance (p<0.05)

Table 4: Culture between Cases and Controls at day 14

Organism	Case		Control		p value
	N	%	N	%	
Citrobacter	5	12.5%	9	22.5%	0.332
E.Coli	5	12.5%	5	12.5%	
Klebsiella	7	17.5%	8	20.0%	

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Pseudomonas	4	10.0%	4	10.0%	
S.Aureus	7	17.5%	10	25.0%	
Sterile	12	30.0%	4	10.0%	
Total	40	100.0%	40	100.0%	

Table 5: Mean Duration of Hospital Stay between Cases and Controls

Parameters	Case		Control		p value
	Mean	SD	Mean	SD	
Hospital Stay (Days)	21.3	6.2	26.7	6.4	<0.001*

Note: * significant at 5% level of significance (p<0.05)

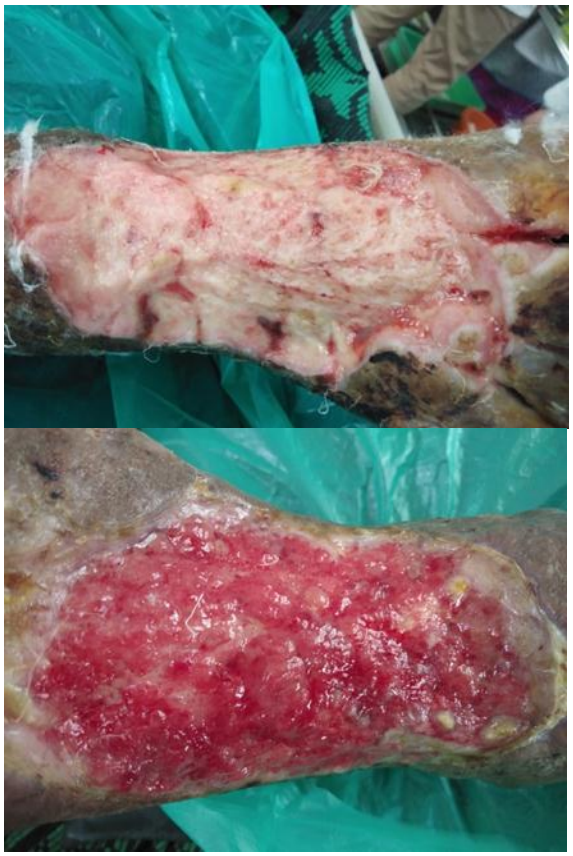

Figure 1: a. (day0), b. (day14) after topical heparin treatment

DISCUSSION

Diabetic ulcers are chronic wounds, stuck in inflammation phase and show a cessation of epidermal growth. An ideal dressing is one that promotes chronic ulcer healing without any complications. Successful wound dressing should keep the wound devoid of any adverse reactions such as infection, maceration and allergy.

The present study was conducted to compare the efficacy of heparin dressings (Cases) with conventional dressings (Controls) on diabetic ulcer healing dynamics.

The mean age of the patients in the Cases group was 57.1 years, which was not significantly different from the mean age of patients (54.0 years) in the Control group.

In the present study, it was seen that the incidence of diabetic ulcers was more among the males in the Cases as well as Controls (85.0% and 75.0 % respectively). The difference in the distribution of sex among the groups was not statistically significant (p= 0.264)

A study by Srinivas and Muralidharan in Tamilnadu, India, also reported a higher incidence of diabetic ulcers among males in the Cases as well as Controls (84.4% and 75.0%).[4]

The National Hospital Discharge Survey of the Centre for Disease Control in the US documented higher hospital rates in males suffering from diabetic ulcers.

By day 14, a reduction of 10% was observed in the surface area of ulcer in Cases as compared to a decrease of 6% in Controls. Both these decreases were found to be statistically significant (p<0.001) suggesting that topical application of heparin enhances wound healing in diabetic ulcers [Table 1].

In a similar Case-Control study, Srinivasan and Muralidharan have also reported a lower Bates - Jensen wound healing score for Cases as compared to Controls at the end of week three and week 4.[4]

The proliferative phase of wound healing is typified initially by the formation of granulation tissue, followed by re-epithelialization, and neovascularisation. Healthy granulation tissue is an indicator of recovery. Once granulation tissue fills the wound to the level of the original epithelium; the epithelia can proliferate and regenerate.

In the present study, by the end of 7 days, healthy granulation tissue was seen in 50% Cases as compared to just 27.5% in Controls. This difference was statistically significant. Similarly by the end of day 14, healthy granulation tissue had developed in 92.5% Cases as compared to 67.5 % Controls who had developed a healthy granulation tissue. This difference between the two groups was statistically significant (p<0.005) [Table 2].

Heparin enhances Type 1 collagen synthesis, and hence the stable granulation tissue causes better healing. Heparin also promotes migration of capillary endothelial cell and produces angiogenesis and thus the formation of healthy granulation tissue.[13,14,15]

The serous fluid contains sugars, white cells, proteins, and other chemicals that are vital in the healing process to move across the wound site. Seropurulent wound drainage is a sign that the wound is becoming colonized and treatment changes are needed.

In the present study, by the end of 7 days, 50% Cases had serous wound discharge as compared to 25 % Controls who had a serous wound discharge. The rate at which the Cases group had serous wound

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discharge was significantly faster as compared to the Control group (p<0.001). By the end of 14 days, 92.5 % Cases had serous wound discharge as compared to 70.0 % Controls who had serous wound discharge. This difference among the groups was statistically significant (p = 0.010). By 21 days, all the Cases, as well as Controls, had serous discharge [Table 3].

In the present study, by the end of 14 days, the culture sensitivity of the wound was done for both Cases as well as Controls. It was observed that in the Cases, a sterile culture was obtained in 30.0 % patients by the end of 14 days, while in Controls only 10% patients showed sterile culture by the end of 14 days. The microorganisms colonizing the wounds were not significantly different among the Cases and Controls [Table 4].

Srinivasan and Muralidharan have reported lower requirement of antibiotic and fewer changes in antibiotics in the Cases as compared to Controls as the sterile culture was obtained earlier in Cases as compared to Controls, similar to our study.[4]

Heparin reduces bacterial translocation,[16] thereby promoting a sterile culture early in the healing process and minimizing the need for antibiotics.

The mean duration of hospital stay was significantly lower for the Cases as compared to Controls (21.3 days ± 6.2 days vs 26.4 days ± 6.4 days, p<0.001) [Table 5].

A similar study by Srinivasan and Muralidharan reported a lower mean hospital stay for Cases as compared to Controls (13.6 days vs 16.4 days, n=32 in each group). However, the statistical significance was not reported for the study.

Thus, in the present study, the group having the application of heparin dressing showed significantly better granulation tissue development, faster reduction of ulcer area and shorter duration of hospital stay, as compared to conventional dressing using povidone iodine. The topical application of heparin results in faster healing.

CONCLUSION

40 patients with diabetic ulcers of Grade 1 and 2 were managed with topical dressing of heparin solution and were compared to the ulcer management in 40 patients with conventional dressing i.e 10% povidone iodine solution. Serial examination of ulcers has shown significant reduction in the ulcer surface area with appearance of healthy granulation tissue, decreased length of hospital stay in patients treated with topical heparin solution as compared to conventional dressing.

However, additional successful clinical evidence is required with validated laboratory findings to establish topical application of heparin solution as one of the most effective alternative topical agents in treatment of diabetic ulcers.

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