Section: General Surgery

Original Research Article

CLINICAL STUDY TO COMPARE THE EFFECTIVENESS OF TOPICAL INSULIN VERSUS TOPICAL PHENYTOIN APPLICATION IN HEALING OF CHRONIC DIABETIC ULCERS

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Abstract

Background: Chronic diabetic foot ulcer is a common disease seen routinely which leads to disability and adds on to the economic burden. Ulcer care has come a long way with various types of dressings and supportive treatment. Our goal was to study the most cost effective, readily available mode of ulcer care in tertiary care centre which promotes early healing of the wound. **Aim and Objective:** To compare the efficacy of topical insulin versus topical phenytoin in chronic diabetic ulcers in terms of rate of wound healing (reduction in size of ulcer), granulation tissue formation and quality of graft bed for skin grafting. **Materials and Methods:** A comparative prospective study of 60 admitted Patients ,40 male and 20 female patients, with chronic diabetic ulcers who fulfilled the criteria were selected and were treated with topical insulin / topical phenytoin dressing. The patients were divided into two groups: Group A (Insulin group) (n=30) and Group B (Phenytoin group) (n=30). Final wound area was measured on 30th day. Comparison between the wound size reduction among two groups done at end of 30th day. Outcome was measured in terms of rate of wound healing (wound size reduction), granulation tissue formation and quality of bed for skin grafting between the two groups. **Results:** In the present study, in Group A (Topical Insulin) Mean ulcer size reduced from 13.75cm2 to 8.03cm2 , and in Group B (Topical Phenytoin) Mean ulcer size reduced from 13.66cm2 to 9.26cm2 after 30 days, The mean percentage reduction in ulcer size in group A was 42% compared to 31% in group B which was statistically significant. The quality of the ulcer bed was good in 86.67% patients with negative pus culture report in Group A compared to 76.67% in Group B. **Conclusion:** Topical insulin is a more efficient and , readily available alternative to topical phenytoin in patients with chronic non healing diabetic ulcers which promotes faster healing of ulcers.

INTRODUCTION

Diabetis mellitus has been a global burden and the number of diabetics is set to increase to 592 million by 2035 as per International diabetes federation.[1] In India 77 million individuals are estimated to have diabetes in 2019, and is expected to rise to over 134 million by 2045.[2] The lifetime risk of developing a diabetic foot ulcer is between 19% and 34%.[3] Foot ulcer preceded in 85% of diabetic patients who had lower extremity amputations.[4] It is estimated that approximately 40,000 legs are being amputated every year in India, of which 75% are neuropathic with secondary infection, which is potentially preventable.[5] Pseudomonas aeruginosa and Staphylococcus aureus were the predominantly isolated organisms, and Candida was the predominantly isolated fungus in diabetic ulcers.[6,7] The phases of wound healing include hemostasis, inflammation, Proliferation and remodeling which depends on cytokines, growth factors and extracellular components. This process of wound healing will be impaired in Diabetes mellitus mainly due to dysfunction of micro and macro circulation

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and peripheral neuropathy. Other causes include chronic inflammation, hyperglycemia, hypoxia and impaired neuropeptide signaling.[8]

Insulin is a peptide hormone and growth factor that can restore damaged skin.[9] It acts by modifying inflammation, accelerating epithelialization and neovascularization.[10] Topical Insulin acts by enhancing anti serine threonine kinase and anti-phosphor extracellular signal regulated protein kinase which helps in faster wound healing.[11]

Phenytoin, an anticonvulsant medication, was noted to have side effect of gingival hyperplasia due to connective tissue growth.[12,13] This very property was studied later and used as an advantage to promote wound healing. Phenytoin enhances collagen deposition, neovascularization, granulation tissue formation, fibroblast proliferation and also has an antibacterial activity and provides local pain relief .[4-17]

Although there are various studies showing the efficacy of topical insulin and topical phenytoin on diabetic ulcers individually, very few studies are available comparing the both. Hence this study was done to investigate whether topical insulin application versus topical phenytoin application has a role in the process of wound healing. This would provide a clinically and economically beneficial method to accelerate the process of wound healing.

MATERIALS AND METHODS

The study was a prospective comparative study that was conducted in the Department of General Surgery Rajarajeswari Medical college and Hospital, Bangalore, between October 2018 to October 2020 after obtaining approval from Ethics Committee [RRMCH-IEC/78/2018-19] A written informed consent was taken from the study participants before enrolling them into the study. The study included 60 patients who presented with chronic Diabetic ulcers chosen by purposive sampling technique. Complete detailed history, physical evaluation, relevant blood investigations, radiological investigations on patients were done and then grouped accordingly.

Inclusion Criteria

- Diabetic patients age 18 years and above
- Chronic Diabetic non-healing ulcers of size more than or equal to 10 cms.
- Grade I and II ulcers of Wagners Classification

Exclusion Criteria

- All diabetic ulcers with acute infections of less than 6 weeks duration.
- Grade III, IV, V ulcers of Wagners Classification
- Doppler showing gross venous abnormalities like varicosities.
- Patients receiving corticosteroids, immunodeficiency (HIV positive, HBsAg positive), immunosuppressive agents, radiation, or chemotherapy.
- Patients who were allergic to phenytoin.
- Patients not willing to enroll in the study

Methodology

Based on the envelop method, patients were divided into two groups of 30 patients each that is group A (topical insulin) and group B (Topical Phenytoin sodium).

Group A (Topical Insulin) Protocol

10 IU of Human Actrapid were applied topically for each 10 cm2 of ulcer daily once at the time of dressing. GRBS were checked 1 hour after dressing for all Group A patients to check for hypoglycemic episode after application of topical insulin.

Group B (Topical Phenytoin Sodium) Protocol

In Group B, one 100 mg Phenytoin sodium tablet is opened and placed in 5ml of sterile normal saline to form a suspension. Sterile gauze was soaked in the suspension and placed over the wound at 20 mg/cm2 surface area. The dressing was changed everyday

After the initial assessment was complete, patients were divided into the Group A and Group B. In Group A, one cc normal saline with 10 IU insulin (Purified human biosynthetic neutral plain insulin) for each 10cm2 wound was used and topical sprayed over wound. The dressing was changed every day. In Group B, one 100 mg Phenytoin sodium tablet was opened and placed in 5ml of sterile normal saline to form a suspension. Sterile gauze was soaked in the suspension and placed over the wound at 20 mg/cm2 surface area. The dressing was changed every day. Daily dressings were done in both groups. Whenever needed a through surgical debridement was done. GRBS was monitored so that the test group patient did not have hypoglycaemia. The ulcers in both the groups were inspected after removal of dressing and were analysed. Size of the wound calculated by multiplying the maximum perpendicular length by the maximum width of the wound bed by measuring tape after tracing the wound margins on a sterile paper and typically recorded in cm2. For the granulation tissue, presence or absence of slough and the type of granulation was noted. The microbiological profile as to whether monomicrobial or polymicrobial was also studied and outcome was measured in terms of wound reduction, granulation tissue formation between the two groups at the end of each week and recorded. Final wound area was measured on 30th day. Comparison between the wound size reductions among two groups was done at end of 30th day.

Statistical Analysis

The data was entered and tabulated in Microsoft excel sheet. Appropriate descriptive statistical tests were used to describe the data. Categorical variable was presented as proportion or percentage. Continuous variable was summarized as mean with standard deviation. Data was analysed using SPSS version 22. Descriptive statistics mean, standard deviation, frequency, percentage was reported for quantitative and qualitative variable. Necessary

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inferential statistics Unpaired t test /Chi- Square test was performed to find out the association between dressing with saline and insulin. A p value < 0.05 was considered significant.

RESULTS

Table 1: Distribution of Age in participants

Group	Group A	Group B	TOTAL	Group A	Group B
30-40 YEARS	7	3	10	23.33%	10.00%
41-50 YEARS	8	6	14	26.67%	20.00%
51-60 YEARS	7	8	15	23.33%	26.67%
61-70 YEARS	5	8	13	16.67%	26.67%
>70 YEARS	3	5	8	10.00%	16.67%

As per table 1 the mean age in the Group A was 52.53 SD+ 12.57 years and in the Group B was 58.83 SD+ 12.5 years. In the present study the age group ranged between 36 years and 80 years the most common age group was between the age of 51-60 years with 15 cases.

Table 2: Gender Wise Distribution

GENDER	**GroupA**	**GroupB**	**TOTAL**	**Group A**	**Group B**
MALES	19	21	40	63.33%	70.00%
FEMALES	11	9	20	36.67%	30.00%
FEMALES	11	9	20	36.67%	30.00%

As per table 2 Our study included 40 males and 20 females with a male to female ratio 2:1.

Table 3: Glycosylated Hemoglobin and Comparison

Group	**Group A**	**Group B**	
Mean	8.117	8.173	p = 0.86
SD	1.250	1.374	
SEM	0.228	0.251	
N	30	30	

The mean HBA1C in the Group A was 8.11 SD+ 1.2 % and in the Group B was 8.17 SD+ 1.3 %.

Table 4: Fasting blood sugar

Group	**Group A**	Group B	
Mean	140.40	137.60	p = 0.55
SD	20.87	15.08	
SEM	3.81	2.75	
N	30	30	

The mean FBS in the Group A was 140 .4 SD+20.87 mg/dl and in the Group B was 137.60 SD+ 15.8 mg/dl.

Table 5: Pus Culture on Day 0 and Day 30

Group	**Group A Day 0**	**Group B Day 0**	**Group A Day 30**	**Group B Day 30**
Positive	28	27	4	7
Negative	2	3	26	23
N	30	30	30	30

The pus culture and sensitivity report on day 30 showed group A – 4 patients showed repeat positive culture remaining 26 patients showed no growth and group B - 7 cases showed repeat positive culture growth , remaining 23 patients showed no growth.

Table 6: Ulcer Size On Day 0

Group	**Group A**	**Group B**	
Mean	13.7517	13.6613	p = 0.88
SD	2.0086	2.4879	
SEM	0.3667	0.4542	

As per table 5 Size of the ulcer on day 0 with group A mean is 13.75 cms and group B is13.6 but it was not statistically significant.

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Table 7: Ulcer Size On Day 30

Group	Day 30 comparison		
	Group A	Group B	p = 0.11
Mean	8.031333	9.266	
Median	7	8.955	

As per table 6 Size of the ulcer on day 30 showed group A mean8.031 cms and group B mean 9.266 cms it was not significant.

Table 8: Reduction in The Ulcer Size Percentage

REDUCTION IN THE ULCER SIZE PERCENTAGE	Group A	Group B	
Median	45%	35%	P= 0.04
Mean	42%	31%	
Std dev	14%	20%	

As per table 7 there is statistical significance between the two groups with percentage reduction size of the ulcer in day 30 with group A mean is 42% and group B is 31% with a p value less than 0.05.

Table 9: Quality of Ulcer Bed

Group	Group A	Group B	TOTAL	Group A	Group B
GOOD	26	23	49	86.67%	76.67%
NOT SATISFACTORY	4	7	11	13.33%	23.33%
TOTAL	30	30	60	100.00%	100.00%

DISCUSSION

Diabetes mellitus is the major healthcare problem worldwide. India is nick named as the diabetic capital of the world.[18] Foot complications in diabetes are a leading cause of global burden of disability.[19] and also the readmission rate is approximately 40% in these patients.[20] Diabetic ulcer care include both systemic and local wound management which comprises of adequate control of blood glucose level, improving the nutritional status of the patient, control of infection, wound debridement, foot off loading , moist ulcer care and adjective treatment options like hyperbaric oxygen, negative pressure wound treatment subject to availability and affordability .

Various studies have shown the efficacy of topical insulin.[10,21,22] and efficacy of topical phenytoin.[14-17] in aggelerating wound healing. Both are cost effective alternatives available for wound dressings. This study was an attempt to compare the benefits of these modalities of treatment in diabetic foot ulcers.

In this study maximum number of patients belonged to age between 51-60years. Male predominance was noted in ulcer cases with male to female ratio of 2:1. The age and gender distribution of cases were similar to other studies of diabetic foot ulcers.[21,22] The ulcer size in Group A reduced from 13.75cm2 on day 0 to 8.031cm2 on day 30 , where as in group B ulcer size reduced from 13.66cm2 on day 0 to 9.26cm2 on day 30. The Percentage reduction of ulcer size was 42% in group A and 31% in group B which was statistically significant. The quality of the ulcer bed was good in 26 patients in group A with good granulation tissue and negative culture and 23 patients in group B had good quality of ulcer bed with negative culture growth. These findings of our study was comparable to studies by Rao MS et al 23and Nagaraj J et al.[24]

In the study by Rao MS et al.[23] where the ulcer healing assessment was after 8 weeks, which was twice the time compared to present study, in group A (topical insulin) mean size of the wound reduced from 6.8 cm2 to 1.4 cm2; percentage change in the size of the wound was 79.4%. In group B (topical phenytoin), mean size of the wound reduced from 5.9 cm2 to 2.4 cm2; percentage reduction in the size of the wound was 59.3%. In group C (normal saline dressing) the mean size of the wound was reduced from 7.1 cm2 to 4.2 cm2; percentage reduction was 40.8%. They concluded that local installation of insulin in the diabetic foot ulcer is better than topical phenytoin and phenytoin is effective than convention wound dressings.

In the study by Nagaraj J et al.[24], the mean difference in wound size before and after treatment in the insulin, normal saline, and phenytoin groups was 4.98, 3.74, and 3.805 square centimetres respectively. The mean difference in wound depth before and after treatment in the insulin, normal saline, and phenytoin groups was 47.005, 4.945, and 4.820 square centimetres, respectively. The mean number of days taken for wound healing in the insulin, normal saline, and phenytoin groups was 20, 26, and 23 days, respectively. The difference in mean for wound size, depth and duration of wound healing in all 3 groups were statistically significant ($P < 0.001$). Hence they concluded that wound healing was better in the local insulin group than in the other two groups.

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CONCLUSION

Based on the findings of our study, it is seen that topical insulin application showed significant difference in terms of percentage of the ulcer size reduction (rate of healing) and faster granulation tissue formation when compared to topical phenytoin application in chronic diabetic ulcers. However there is no significant difference between the two modalities of management in respect to quality of bed for skin grafting. Hence it can be concluded that Topical insulin is a more efficient and, readily available alternative to topical phenytoin in patients with chronic non healing diabetic ulcers which promotes faster healing of ulcers. The limitation of the study is that, its of smaller sample size and further studies are recommended with larger sample size and longer duration to see the long term benefits and adverse effects between topical insulin versus topical phenytoin application in chronic diabetics.

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