
**E-ISSN: 2616-3470**
**P-ISSN: 2616-3462**

www.surgeryscience.com
2019; 3(1): 26-32
Received: 23-11-2018
Accepted: 25-12-2018

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# A comparative study between topical insulin versus normal saline dressings in wound healing in diabetic foot ulcers

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**DOI:** https://doi.org/10.33545/surgery.2019.v3.i1a.09

**Abstract**
**Introduction:** Diabetic foot ulcer (DFU) is the most costly and devastating complication of diabetes mellitus, which affect 15% of diabetic patients during their lifetime. The purpose of this prospective study was to investigate the efficacy and safety of topical insulin in management of patients with diabetic foot ulcers.
**Materials and methodology:** 74 patients were included in the study. 37 in the group A i.e. topical insulin dressing group & 37 in the group B i.e. normal saline dressing group. Initial wound debridement followed by wound measurements were done on day 1, 7 & 15. Reduction in wound area at end of day15 was compared.
**Results:** There was statistically significant reduction in the area of ulcer at end of day 15 (p value <0.001).
**Conclusion:** The use of topical insulin is safe and efficacious in treatment of diabetic foot ulcers.

**Keywords:** Diabetes mellitus, diabetic foot ulcer, topical insulin, efficacy

## Introduction
Diabetes Mellitus is known to be one of the oldest diseases in the world. There has been a continuous increase in the prevalence of diabetes worldwide at a frightening rate due to change in lifestyle, obesity and physical inactivity.
78 million people in South east Asian region are affected by diabetes mellitus and is expected to attain 140 million by 2040. WHO reports that, India had 69.2 million people living with diabetes (8.7%) as per the 2015 data, among these more than 36 million people remained undiagnosed [1].
Diabetes Mellitus (DM) is a metabolic disorder which lead to microangiopathy and macroangiopathy causing nephropathy, neuropathy, retinopathy, peripheral vascular disease, atherosclerosis and infections.
Diabetic foot ulcers (DFU) are one of the major complications of diabetes. Despite proper insulin treatment and a strict diabetic diet, 15% of diabetic population develop non-healing ulcers which lead to amputations of the lower limb significantly [2].
Diabetic foot ulcer is considered as a major source of morbidity and a leading cause of hospitalization in patients with diabetes [3, 4, 5, 6]. It is estimated that approximately 20% of hospital admissions among patients with Diabetes Mellitus (DM) are the result of DFU [7].
It is estimated that approximately 50%-70% of all lower limb amputations are due to DFU. In addition, it is reported that every 30seconds, one leg is amputated due to DFU in worldwide [8].
Management of diabetic foot ulcers includes control of existing infection by diligent antibiotic administration, local wound care, offloading the wound with use of proper therapeutic footwear, wound debridement (in case of presence of necrotic tissue), control of blood sugar levels and assessment of peripheral arterial state.
In the present day there are various types of dressings available and these form a pivotal part in the healing of foot ulcers. Topical dressings comprise as one of the modalities of care for diabetic foot ulcers. Different types of moist dressings and topical agents are used in the modern day for wound healing.
Topical Insulin has proved to be efficacious in promoting wound healing by activating serine-threonine kinase (AKT) and extracellular signal regulated protein kinase (ERK) pathway [9].
Research consistently highlights the importance of the insulin receptor, a transmembrane molecule, activated by insulin, IGF-I and IGF-II. It belongs to a large class of tyrosine kinase receptors found in all cell types, including keratinocytes and fibroblasts [10].

Liu, *et al*. [11] showed that topical application of insulin to excision wounds stimulates keratinocyte migration. This migratory enhancement involves the PI3K-Akt pathway, and identifies Rac1, a small GTPase, as a molecule activated downstream of PI3K-Akt [12].

Lima *et al*. [13] showed that insulin signalling pathways are promoted in the injured skin of normal rats, whereas these pathways are attenuated in diabetic animals due to insulin deficiency. However, when injured skin of diabetic rats is treated with a topical insulin cream, an acceleration of wound healing occurs, together with a recovery in the proteins of the insulin signalling cascade [14]. Therefore, expression of proteins involved in the early phase of insulin exposure, namely, IRS-1,2 and Akt, are increased in healing tissue when compared to healthy skin.

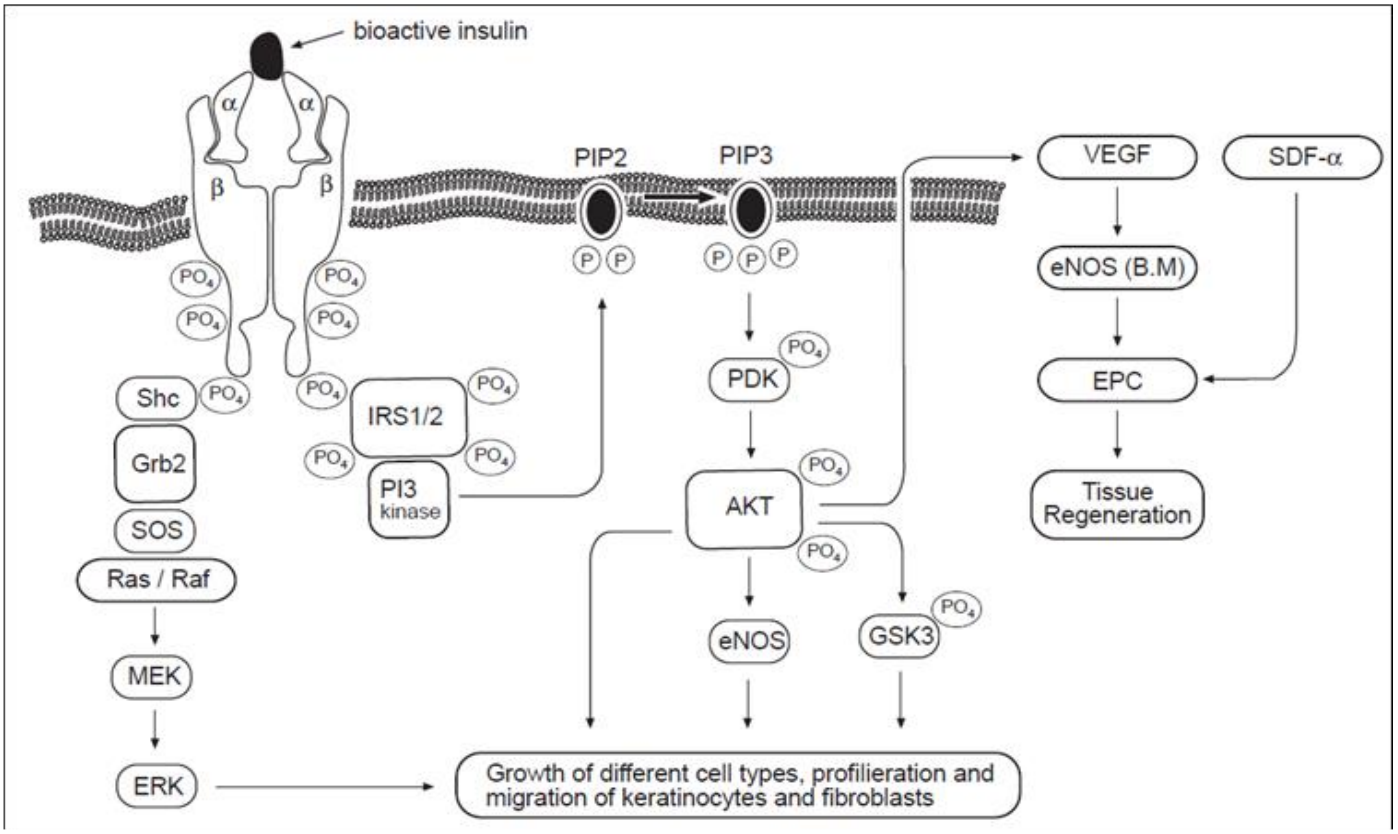


**Fig 1:** Effect of insulin on cellular and molecular mechanisms of wound healing. Insulin induces activation of IR/IRS/PI3K/AKT pathways. On the upper right-hand side, AKT is shown to increase VEGF that will induce the phosphorylation and activation of eNOS in bone marrow, with consequent mobilization of EPCs to the circulation, where they participate in tissue regeneration.

**Materials and methodology**

This is a prospective study which was conducted in Karnataka institute of medical sciences, Hubli in the department of General surgery from December 2016 till July 2018. Our aim was to prove that topical insulin application is safe and efficacious in diabetic foot ulcers.

**Inclusion Criteria**

All recently diagnosed patients with diabetic foot infections who are above 18 years and who are presenting for the first time.

**Exclusion Criteria**

Patients who have been operated for Diabetic foot infections earlier (in the same foot),

Ulcers of Wagner's grade III with osteomyelitis, grade IV which requires amputation(major) and grade V, X-rays showing features of osteomyelitis, Doppler showing gross atherosclerotic arterial changes and venous abnormalities like varicosities of lower limbs, Uncontrolled diabetes with HbA1C levels >8.

**Procedure**

Patients with diabetic foot ulcers who underwent debridement as a fresh case are non-randomly selected into two groups i.e. case and control group. In case group, ulcers are cleaned with normal saline and then 4 units (0.1 ml) of Human mixtard insulin in 1 ml normal saline (0.9%) for each 10 cm2 of wound is applied once daily. The solution prepared in insulin syringe is sprayed on sterile cotton gauzes which are applied over the ulcer area. In control group, ulcers are cleaned with normal saline without insulin and covered with sterile gauzes.

All patients are treated empirically with Inj. Amoxycillin-clavulanic acid 1.2g IV bd, Inj. Metronidazole 100 ml IV tid at the time of admission. Later antibiotics are changed according to pus culture and sensitivity reports.

Wounds are measured using a sterile transparent gauze placed on the wound to mark the wound borders. The two largest perpendicular diameters are measured using a ruler (in centimetres). To calculate the wound area, these two diameters are multiplied to obtain area of ulcer in $cm^2$. Even though topical Insulin is not absorbed systemically, to evaluate the safety, random blood glucose levels are measured with a glucometer 10 minutes before and 1 hour after application of topical insulin in case group patients.

Ulcer size is measured on day1, day7 and day 15. Reduction in the area of ulcer is calculated at day 7 and day 15 in comparison with day 1 area of ulcer measured in $cm^2$. End of 15 days, we are comparing the rate of epithelisation of the ulcer in terms of reduction in the area of ulcer on day 7 and day 15.

## Results

Data were entered in Microsoft Excel and analysed using Stata version 14. Continuous variable, age was expressed as mean (standard deviation). The distribution of categorical variables like age categories, gender was expressed as proportions. The comparison of distribution of gender, grade, limb and Doppler findings between cases and controls were assessed using a chi-squared test. The comparison of effectiveness between the cases and controls based on length, breadth, area and reduction of area at different time point (Day1, Day 7 and Day 15) were assessed using an independent t test or Mann Whitney U test/ Wilcoxon Rank sum Test based on its distribution. The comparison of safety measures such as albumin, haemoglobin, HbA1C, total count, doppler of the affected limb and organisms cultured from the wound site between the cases and controls were assessed using an independent t test. A p value of less than 0.05 was considered as statistically significant.

Total 74 patients were included in the study who were admitted in Karnataka institute of medical sciences Hubli from December 2016 till July 2018. Patients were nonrandomly selected into two groups i.e. case and control group. Each group has 37 patients.

Out of 37 patients in case group mean age was 47.8 years, 22 of them were aged below 50 years and 15 people were aged more than 50 years. Out of 37 in control group mean age was 59.4 years, 10 people were aged below 50 years and 27 people were aged above 50 years. 24 people in case group were male patients whereas 23 in control group out of 37 patients.

Most common involved limb was right lower limb i.e. 40 patients in total study group. Ulcers were classified basis on Wagner's grading of the diabetic foot ulcers. Only grade 1 & 2 were included in the study. Most of the ulcers were grade 2 in both groups i.e. 21 in case group & 28 in control group.

Out of 74 patients in the study, 37 did not require any amputations. i.e. any minor amputations. But other 37 required amputations in the form of Ray's amputation of toes which were included in the study. In case group 25 patients had underwent minor amputation.

Most common organism isolated from wound culture in the study was E. coli followed by staph aureus & proteus species. Pseudomonas was noted only in the control group.

**Table 1:** Comparison of Length on day 1, 7 and 15 within the Groups (N=10)

| Group | Number | Mean (SD) Length | | | P Value |
|---|---|---|---|---|---|
| | | Day 1 | Day 7 | Day 15 | |
| Cases | 37 | 5.5 (1) | 5.3 (1) | 5 (1) | 0.049 |
| Controls | 37 | 6.2 (1.3) | 6.1 (1.3) | 5.9 (1.2) | 0.66 |

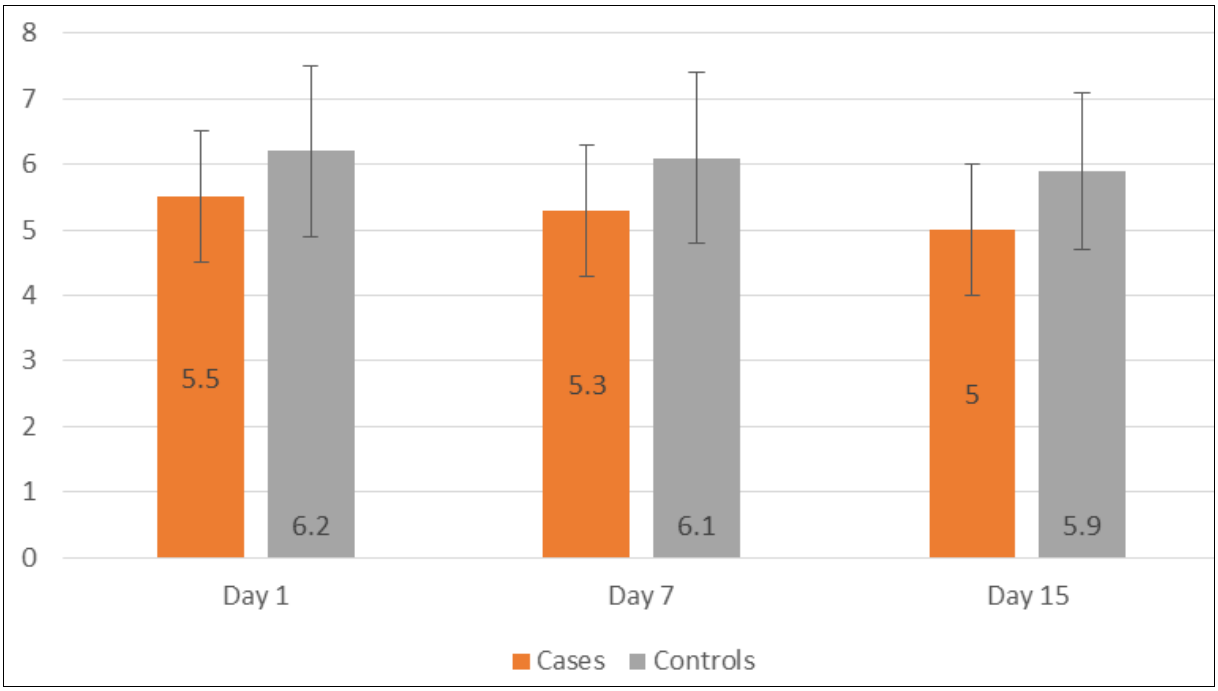


**Fig 2:** Comparison of Length on day 1, 7 and 15 within the Groups

The table 1 & figure 2 shows mean length of ulcer in both groups measured on day 1. 7 and day 15. There was statistically significant decrease in length in case group with p value of 0.049.

**Table 2:** Comparison of Breadth on day 1, 7 and 15 within the Groups (N=10)

| Group | Number | Mean (SD) Breadth | | | P Value |
|---|---|---|---|---|---|
| | | Day 1 | Day 7 | Day 15 | |
| Cases | 37 | 3.4 (0.8) | 3.2 (0.8) | 2.9 (0.8) | 0.013 |
| Controls | 37 | 4.1 (0.9) | 4 (0.9) | 3.8 (0.9) | 0.43 |

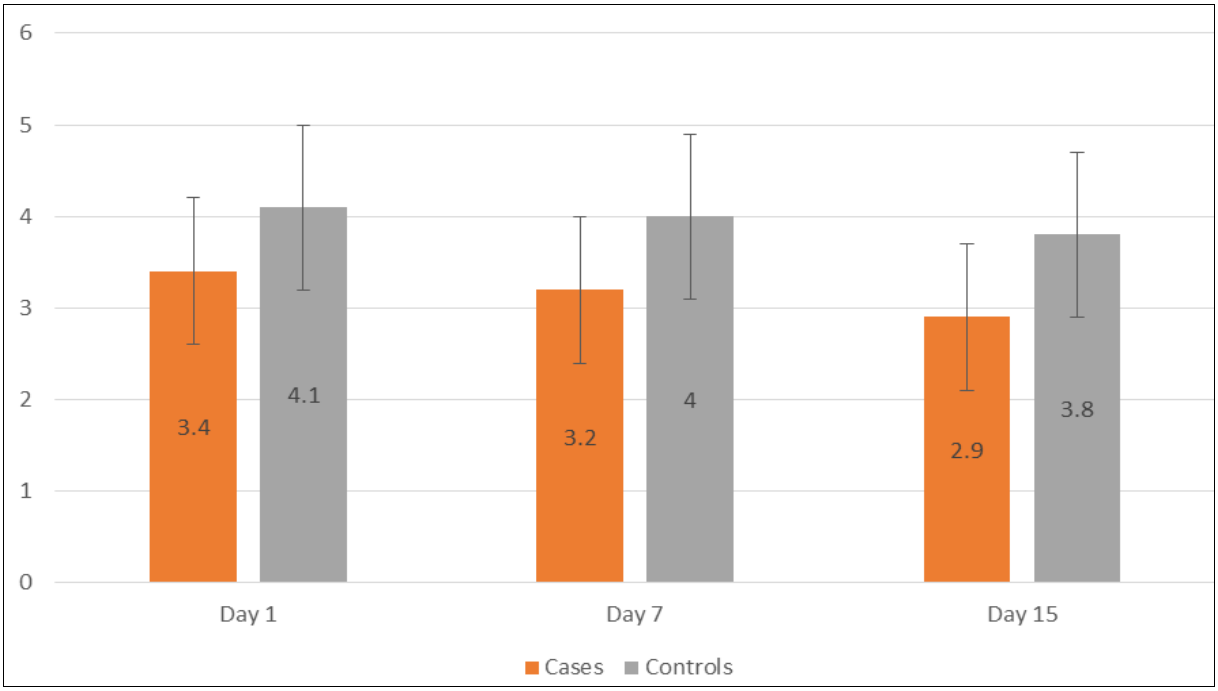


**Fig 3:** Comparison of Breadth on day 1, 7 and 15 within the Groups

The table 2 & figure 3 shows mean breadth of ulcer in both groups measured on day 1, day7 & day 15. There was statistically significant decrease in the breadth of ulcer with p value of 0.013 in case group as compared to control group**.**

**Table 3:** Comparison of Area at day 1, 7 and 15 within the Groups (N=10)

| Group | Number | Mean (SD) Area | | | P Value |
|---|---|---|---|---|---|
| | | Day 1 | Day 7 | Day 15 | |
| Cases | 37 | 19.4 (7.2) | 17.3 (6.9) | 14.7 (6.5) | 0.015 |
| Controls | 37 | 26.2 (11.2) | 25 (11) | 23.5 (10.5) | 0.56 |

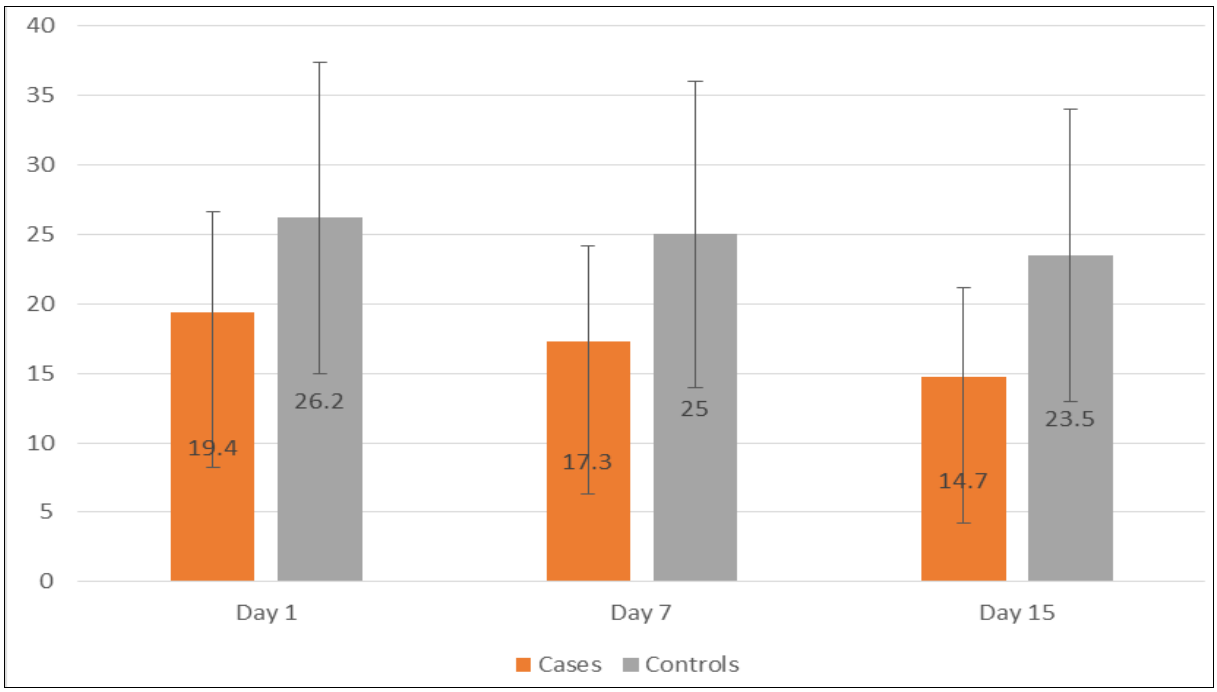


**Fig 4:** Comparison of Area at day 1, 7 and 15 within the Groups

The table 3 & figure 4 shows comparison of area of the ulcer measured on day 1, day 7 and day15 in both groups. Statistically significant changes seen in area of ulcer in case group measured on day 7 and 15 compared to control group with p value of 0.015.

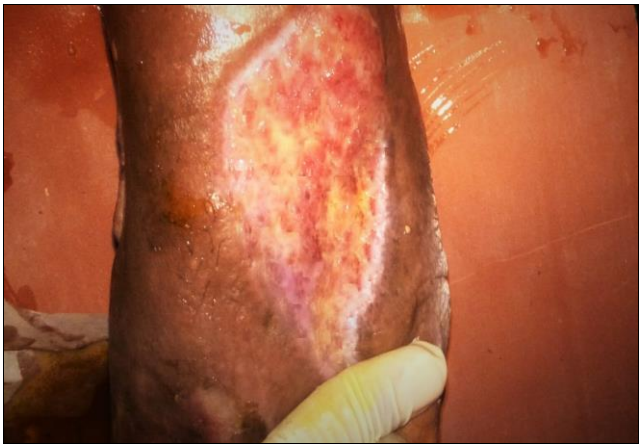

**Fig 5:** Day 1 of ulcer in insulin group

**Fig 6:** Day 15 of ulcer in insulin group

**Fig 7:** Day 1 of ulcer in normal saline group

**Fig 8:** Day 15 of ulcer in normal saline group

**Fig 9:** Day 1 of ulcer (post ray's amputation of 5$^{th}$ toe) in insulin group

**Fig 10:** Day 15 of ulcer (post ray's amputation of 5$^{th}$ toe) in insulin group

**Discussion**

Foot ulcers in patients with diabetes is common, and frequently leads to lower limb amputation unless a prompt, rational, multidisciplinary approach to therapy is taken.

Foot ulceration in diabetic patients is a resource consuming, disabling morbidity that often is the first step towards lower extremity amputation. Prevention is the best treatment.

The hallmark of diabetic foot problem in our populations is gross infection, and major contributing factors for late presentation include bare foot gait, attempts at home surgery, trust in faith healers and undetected diabetes.

Diabetic patients have always suffered from complications affecting the lower limbs. Foot infection and the subsequent amputation of a lower extremity are the most common cause of hospitalization among diabetic patients.

In our study, most common patients were male farmers who had history of trivial trauma before wound formation in the foot. Most of them were known diabetic who had borderline controlled sugars. Criteria for inclusion in study group was more selective, hence many rural people were found to be unfit into the study due to late presentation in the form osteomyelitis, ischemia/ gangrene of the foot who ultimately required more than dressing that is major limb amputations.

Topical dressing of the ulcer is one of the modalities in treatment of ulcers. There are many new research methods going on to see the efficacy of various products like hydrocolloids, hydrogels, alginates, impregnated films etc which costs much in the market. Topical insulin is an easier technique which is proved in excellent way comparable to other commercially available applicants in healing of diabetic/ chronic non-healing ulcers.

Mean length of ulcer on day 1 in case group was 5.5 cms, breadth was 3.4 cms & area was 19.4 $cm^2$. On day 7 mean length was 5.3 cms, breadth was 3.2 cms and area was 17.3 $cm^2$. Reduction in area was 2.1 $cm^2$ which was significant with p value of <0.001. Mean length on day 15 was 4.9 cms, breadth was 2.9 cms and area was 14.7 $cm^2$ with mean reduction in area compared to day 1 by 4.7 $cm^2$. In control group mean reduction in area at day 7 was 1.2 $cm^2$ and day 15 was 2.7 $cm^2$ only.

In a study conducted by Swaminathan *et al* [15], the mean ulcer area in insulin group was 4.1 $cm^2$ and in saline group it was 3.1$cm^2$ on day 1. Another study conducted by Sanjay Pandey *et al* [16], the mean ulcer area at the time of admission in group A i.e. insulin group was 4.8 ± 0.6 $cm^2$, 5.35±0.6$cm^2$ in group B i.e. normal saline group. Another study conducted by Amrita prasad *et al*. [17] had, 13 $cm^2$ as the mean ulcer size in insulin group and 14.51 $cm^2$ in control group.

In study conducted by Sanjay Pandey *et al*, the mean difference in surface area of ulcer after 12th day was 3.2±0.7$cm^2$ in group A (insulin group), 2.9±0.8$cm^2$ in group B(normal saline). In a study by Swaminathan *et al*, the reduction in mean ulcer size was 2.5 $cm^2$ in insulin group and 1.0$cm^2$ in saline group after 4 weeks. In the study of Amrita prasad *et al*, at end of 20 days the mean reduction in area of ulcer in insulin group was 4.06 $cm^2$ whereas control group was 3.5 $cm^2$ which was statistically significant.

Comparison of area at day 1, 7 and 15 in case group in our study had p value of 0.015 whereas in control group it was 0.56. Comparison between mean reduction in area at end of day 15 between case and control group had p value <0.01.

**Table 4:** Comparison between other studies done in Indian population

| Study Mean reduction in area of ulcer | Current study (day 15) | Swaminathan *et al* (4weeks) | Sanjay Pandey *et al* (day 12) | Amrita prasad *et al* (day 20) |
|---|---|---|---|---|
| Case group | 4.7 $cm^2$ | 2.5$cm^2$ | 3.2±0.7$cm^2$ | 4.06 cm2 |
| Control group | 2.7 $cm^2$ | 1.0$cm^2$ | 2.9±0.8$cm^2$ | 3.5 $cm^2$ |

## Conclusion

In our study to evaluate the efficacy of topical insulin dressing in diabetic foot ulcers, we conclude that it is effective in early healing of ulcer compared to normal saline dressings. There is statistically significant decrease in mean area of the ulcer at end of day 15.

Our study was comparable to studies done by Swaminathan *et al*, Sanjay Pandey *et al* and Amrita Prasad *et al* in Indian population recently. Although the inclusion & exclusion criteria, the management of wound, the outcome variables, study period vary a little but the main aim in showing the efficacy of topical insulin application in early healing of wounds is comparable.

Topical insulin application could bring down chronicity of dressing in the patients. It did not have any systemic complications. It is cost effective. With effective hemoglobin, albumin, controlled glycemic index, with appropriate antibiotics and well-motivated patient, topical insulin seems to be fair alternative compared to other pharmacological applicants which costs much for the patient.

Topical dressing is not a single-handed approach in healing of ulcers, it is a multidisciplinary team approach which includes good sugar control, foot care, dressings, timely surgical interventions & most of all patient's motivation & education regarding the ulcer care.

In short, Diabetic foot ulcer (DFU) is the most common complication of diabetes mellitus that usually fail to heal, and leading to lower limb amputation. Early effective management of DFU as follows: education, blood sugar control, wound debridement, advanced dressing, offloading, advance therapies and in some cases surgery, can reduce the severity of complications, and also can improve overall quality of life of patients especially by using a multidisciplinary team approach.

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