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Original research article

A study to compare the effect of topical insulin over normal saline in diabetic ulcer foot

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Abstract

The diabetic foot ulcer is the precursor for diabetic foot and it is the most common sequel that occurs following any trauma or infection in a diabetic individual. The diabetic foot ulcers most commonly occur at the distal ends of the extremities because this is the area with the vascularity is the least as a result of microangiopathy that has occurs in in diabetes mellitus. The study was started after the ethical clearance was secured from the institution's ethical clearance committee. Following this the patients who came to the surgical outpatient department and the subspecialties of surgery that dealt with diabetic foot ulcers where well explained regarding the study. After they give informed consent to participate in the study, a thorough physical examination and history was taken based on a pre-defined questionnaire that was semi felt field. We noted that when insulin was used it reduced the size of the wound at a faster rate as compared to the conventional normal saline dressings. Also the quality of granulation tissue and the per cent reduction of the ulcer size was far better in the insulin group. We did not note any adverse effects as a result of insulin use in the test group.

Keywords: Topical insulin, normal saline, diabetic ulcer foot.

Introduction

The term diabetes mellitus refers to a metabolic disorder that is associated with abnormality of insulin production or resistance to with action at the peripheral tissues [1]. Though, this is one of the commonest metabolic disorder that is known it is not the metabolic profile but the complications that it causes which are more worrisome to the clinician [2].

This disease has been known since time immemorial. It has been well known even in ancient Indian texts where it is referred to by various names like madhumeha that is sweet honey it is gaining popularity recently not only because of its increasing incidence but, also because of the fact that the complications associated with it [3].

Complications that are known very well as a consequence of long-term diabetes are diabetic retinopathy, diabetic neuropathy, diabetic microangiopathy [4]. All these three factors have contributed to the increase in the cardiovascular disorders, the cerebrovascular disorders, and the diabetic foot complications that occur in diabetes mellitus [4].

Diabetic foot is one of the well-known surgical problems that a diabetic patient presents to the consultation room. The predisposing factor for development of diabetic foot is the peripheral neuropathy that is associated with diabetes mellitus that causes the patient to lose sensation in the foot making him an aware of minor trauma until it becomes very severe [5, 6].

The diabetic foot ulcer is the precursor for diabetic foot and it is the most common sequel that occurs following any trauma or infection in a diabetic individual. The diabetic foot ulcers most commonly occur at the distal ends of the extremities because this is the area with the vascularity is the least as a result of microangiopathy that has occurs in in diabetes mellitus [7].

It is very important to note that, even though the management of sugars will be very good, it is common to see that at least 15% of individuals at some point in their life will have a non-healing ulcer in the lower extremity which will progress to require and amputation if nor cared for at the right time [8].

The other contributory factors that cause chroncity the ulcer in diabetic mellitus to heal are abnormal wound healing process [9-11].

It is also noted that in diabetics there is a reduction in the production of growth factors that is required for abnormal wound healing to occur.

Also because of the abnormality of accumulation of collagen, defective epidermal barrier abnormality of the macrophage function and the angiogenic response the wounds often tend to not follow the normal

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orderly process of wound healing.
Also, the most important factor that is associated with impairment of wound healing it is the abnormality in the signalling pathways especially, the production of fibroblasts and the cells that are responsible for forming the extracellular matrix and collagen [12].
Various treatments having tried in Diabetic foot in order to improve and accelerate the process. Even topical insulin has been used for this purpose and it is shown in various studies that when and cream of topical insulin is applied topically it can help to activate the various pathways that signal production of collagen.
Also, so it has a stimulatory effect on the production of collagen within the fibroblast that are present inside the skin. It will also activate the proliferation of myofibroblasts thus enhancing the extra cellular matrix production and collagen synthesis.
It also has an action that activates the and stimulates differentiation of the keratinocytes migration and the proliferation of cell.
The insulin is known to act on each and every stage of wound healing especially the ones that are impaired in diabetic patients.
Keeping this in mind we at the medical college teaching centre decided to study the role of topical insulin in patients who have diabetic foot ulcers.

Methodology
Study Design: Hospital based Comparative Observational study.
Sample size: 60.
Sampling Technique: Convenience sampling was adopted to select the individuals for the study.

Inclusion criteria
1. Diabetic patients of age 18 years and above.
2. Patients having ulcers measuring more than one cm.
3. Patients with controlled blood glucose levels.
4. Patients with grade 1 and grade 2 Wegener's classification were selected for the study.

Exclusion criteria
1. Patients with absent peripheral pulses in dorsal pedis artery, posterior tibial artery and anterior tibial artery.
2. Known case of hypersensitivity or allergic reaction to the drug used in study.
3. X-rays showing features of osteomyelitis.
4. Malnutrition and uncontrolled diabetes.
5. Patients receiving immunosuppressive therapy.
6. Patients not giving consent for the dressing.

Methodology
Two groups with 60 people each were taken.
Group A includes normal saline dressing to ulcer.
Group B includes insulin dressing to ulcer.

The daily dressing is done mean area of ulcer is noted before dressing. After 14 days of dressing areas of ulcers are taken in mm square measurements using callipers, compared between the two groups.
The study was started after the ethical clearance was secured from the institution's ethical clearance committee. Following this the patients who came to the surgical outpatient department and the subspecialities of surgery that dealt with diabetic foot ulcers where well explained regarding the study.
After they give informed consent to participate in the study, a thorough physical examination and history was taken based on a pre-defined questionnaire that was semi felt field.
Those who met the inclusion and exclusion criteria were finally chosen for the study. The patients where explained regarding the possible complications and consequences of entering into the study including the side effects of the medications used and if they note the side effects what is the possible remedial measure they need to take and whom to report.
On fully understanding regarding the study their recruitment was done and they were handed a consent sheet to sign to participate in the study and they were given a patient information sheet. Those who chose to participate willingly were randomized into two groups based on the lottery method and.
The group A received the study drug insulin as a topical solution over the wound.
The control group was the group was the patients in whom normal saline was done which is the conventional dressing for a diabetic ulcer ask for the American diabetic association. The patients also underwent investigations that included Doppler to check for the presence of peripheral arterial occlusive disease, urine albumin examination to check for diabetic nephropathy and retinal fundoscopy was done to check for the presence of diabetic retinopathy. If any of the three were present it was documented. The

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patients are also underwent laboratory investigations for evaluation of diabetes. At the time of recruitment the size of the wound was measured three dimensionally by using a skin calipers and the volume of the wound was calculated. After 14 days of initiation of therapy the size was again calculated by the same individual who measured the wound on day one in order to prevent bias. During this 14 days the patient was carefully evaluated for the presence of any adverse events like hypoglycaemic episodes, seizures, bleeding from the wound, discharge from the wound and the type of granulation tissue. Also the number of deployments that were needed and any other secondary procedures that was done was noted. After this the patient was evaluated for any secondary procedures that were done after 14 days and the approximate time for closure of the ulcer was also noted.

Results

Table 1: Duration of Ulcer

Group	N	Minimum	Maximum	Mean	Std. Deviation
G1	60	10	220	61.58	42.918
	60				
G2	60	10	153	64.07	39.119
	60				

Table 2: Grades at Presentation

Group * grade presentation crosstabulation					
			Grade at presentation		Total
			Wagner grade 1	Wagner grade 2	
Group	G1	Count	42	18	60
		Expected Count	41.0	19.0	60.0
		% with group	70.0%	30.0%	100.0%
	G2	Count	40	20	60
		Expected Count	41.0	19.0	60.0
		% with group	66.7%	33.3%	100.0%
Total		Count	82	38	120
		Expected Count	82.0	38.0	120.0
		% with group	68.3%	31.7%	100.0%

Table 3: Procedure

Group * procedure done crosstabulation					
			Procedure done		Total
			Heald spontaneously	Needed additional procedures	
Group	G1	Count	43	17	60
		Expected Count	45.5	14.5	60.0
		% with group	71.7%	28.3%	100.0%
	G2	Count	48	12	60
		Expected Count	45.5	14.5	60.0
		% with group	80.0%	20.0%	100.0%
Total		Count	91	29	120
		Expected Count	91.0	29.0	120.0
		% with group	75.8%	24.2%	100.0%

Table 4: Discharge at day 07

Group * Dl1CHARGE days 07 crosstabuulation						
			Dl1CHARGE days 07			
			No	PUS	Serous	Serousanguinous
Group	G1	Count	5	4	51	0
		Expected Count	3.0	4.0	4.5	8.5
		% with group	8.3%	6.7%	85.0%	0.0%
	G2	Count	1	4	38	17
		Expected Count	3.0	4.0	44.5	8.5
		% with group	1.7%	6.7%	63.3%	28.3%
Total		Count	6	8	89	17
		Expected Count	6.0	8.0	89.0	17.0
		% with group	5.0%	6.7%	74.2%	14.2%

Table 5: Discharge at day 14

Group * Dl1CHARGE days 14 crosstabuulation		Total
	Dl1CHARGE days 14	

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			No	Serous	Serousanguino	
Group	G1	Count	30	30	0	60
		Expected Count	27.5	27.5	5.0	60.0
		% with group	50.0%	50.0%	0.0%	100.0%
	G2	Count	25	25	10	60
		Expected Count	27.5	27.5	5.0	60.0
		% with group	41.7%	41.7%	16.7%	100.0%
Total		Count	55	55	10	120
		Expected Count	55.0	55.0	10.0	120.0
		% with group	45.8%	45.8%	8.3%	100.0%

Table 6: Granulation

Group * Granulation days 10 crosstabuulation						Total
			Granulation days 10			
			PALE	BEEFY RED	PINK	
Group	G1	Count	29	27	4	60
		Expected Count	25.0	32.0	3.0	60.0
		% with group	48.3%	45.0%	6.7%	100.0%
	G2	Count	21	37	2	60
		Expected Count	25.0	32.0	3.0	60.0
		% with group	35.0%	1.7%	3.3%	100.0%
Total		Count	50	64	6	120
		Expected Count	50.0	64.0	6.0	120.0

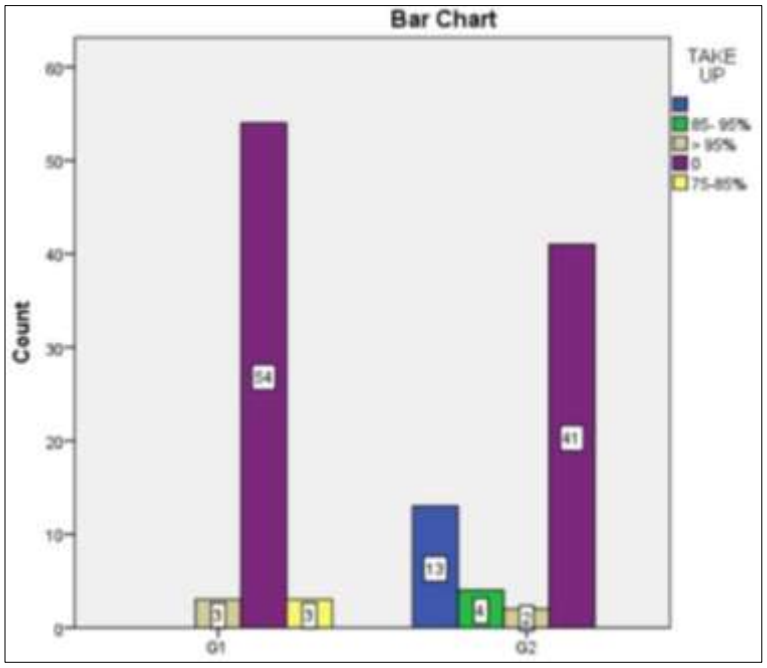

Fig 1: Take up

Discussion

There are a variety of factors that a wound healing in diabetes mellitus and almost all of them can be altered by insulin. Study that was done by Bradley and co-workers the authors suggested that the use of insulin in rules who to stimulate the growth and development of the keratinocytes it's often do TDM and the fibroblastic cells along with helping them to proliferate does helping in healing of tissues.

Maria H M Lima *et al.* [13] saw that when insulin was used as a topical cream of insulin is used on wound healing it helped in acceleration of wound healing by rescuing the proteins increasing the levels especially IR, IRS-1, IRS-2, SHC, ERK, and AKT that are involved in tissue repair at an early stage.

Wang *et al.* [14] noted that when a spray of insulin was used in those ulcers that occurred in diabetic patients an insulin spray-based formulation has been used successfully to treat patients with diabetic ulcers.

Zhang *et al.* [15] 2007 noted that when long-acting insulin zinc suspension was used as a topical application in wounds it helped to enhance the healing process at the site of skin transplant with no systemic complications. The healing on wounds occurred faster than control 11.2±2.3 days in the insulin as compared to 15.1±4.1 days in the control group p + 0. 002.

Zagon *et al.* [16] in the year 2007 noted the healing effect of topical insulin in corneal abrasions when used

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in the form of eye drops in the form off significant reduction in the healing times and enhanced rate of corneal re-epithelisation without any local or systemic adverse effect.

Azevedo *et al*. [17] in the year 2016 noted that in those rats that has sustained second degree burns the rate of heaing, recruitment of inflammatory cells and deposition of collagen is more in them as compared to when the same combination was used in non-diabetic rats.

Van Ort and Gerber [18] in the year 1976 noted that in those patients in whom topical insulin was used in the wounds it resulted in a significant reduction in the size of the wound. They noted that the healing of the wounds took place without any adverse effects like hypoglycaemia.

Rezvani *et al*. [19] in the year 2009 noted that in those individuals who had known infected wounds help to reduce the wound size and enhance the rate of healing 46. 09 mm2/day versus 32. 24 mm2/day p = 0. 029 without any adverse effects.

Attia *et al*. [20] in the year 2014 recorded a better response rate with topicalinsulin as compared to topical zinc with no side effects in either group.

Martinez's *et al*. [21] in the year noted better angiogenesis in acute full thickness wounds as compared to control group with no difference in the rate of fibrosis.

Gaurav Goenka and *et al*. [22] study showed that number of days required for healing was 38±17.03 days in the group of diabetic patients whose ulcers were treated with topcal insulin and 44.3±17.5 days in the group of diabetic patients whose ulcers were treated with normal saline.

Conclusion

We noted that when insulin was used it reduced the size of the wound at a faster rate as compared to the conventional normal saline dressings. Also the quality of granulation tissue and the percent reduction of the ulcer size was far better in the insulin group.

We did not note any adverse effects as a result of insulin use in the test group.

Hence as per the study findings we concluded that in diabetic ulcers the use of topic insulin is preferred to hasten the healing of wounds.

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