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Original Research Article

COMPARATIVE STUDY OF INSULIN WITH ORAL ANTI-DIABETIC DRUG IN TYPE 2 DIABETIC WOUND HEALING

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Abstract

Background: Chronic wounds are a common complication in patients with diabetes that often lead to amputation. Insulin and oral hypoglycaemic agent have been reported to treat diabetic wound healing. The present study was carried out to compare insulin with an oral anti-diabetic drug in treating type 2 diabetic wound healing. **Materials and Methods:** This prospective observational study was conducted from September 2021 to December 2022. Patients aged 45 to 65 years of either gender were taken for the study. Wounds of less than two months on the plantar aspect and less than one month on the dorsum of the foot were selected. All 224 subjects were divided into two groups, namely Group I comprising 124 patients on Insulin therapy and Group II, having 100 patients treated with an oral hypoglycaemic agent (OHA). After the therapy for two weeks mean ulceration area was observed and compared to the initial wound size. **Result:** In the present study, 224 patients, in Wagner's classifications 1 and 2, aged more than 40 and less than 65 years having diabetic ulcer foot, were enrolled for the study. Maximum patients 105 (46.87%) were reported in the age group of 56 to 60. The majority of patients were male in both groups. The maximum ulcer size of 5-10 cm2 was recorded in most patients in both groups. Patients of Group II treated with insulin showed more decrease in mean wound ulcer size than Group I patients treated with OHA. **Conclusion:** In the present study, patients treated with insulin (Group I) showed better wound size healing improvement than those treated with OHA (Group II).

INTRODUCTION

Approximately 150 million patients worldwide have type 2 diabetes, and it has been estimated that type 2 diabetes will affect 300 million people by 2025.[1] Diabetes is associated with impaired wound healing, making patients susceptible to chronic non-healing wounds. Such wounds precede 84% of all diabetic lower extremity amputations, and once amputation occurs, patients have a 5-year mortality rate of 50%.[2]

Chronic diabetic wounds are trapped in a persistent inflammatory state with elevated levels of pro-inflammatory cytokines and proteases and impaired expression of growth factors. At the same time, the CDC reported that out of 20.9 million respondents with diabetes in the National Health Interview Survey, 2.9 million take insulin only, 11.9 million take oral diabetic medications only, 3.1 million take both, and 3 million take none.3 Thus, while over 70% of patients with diabetes take diabetic medications regularly at an annual cost of over $50 billion, little is known about whether these medications influence wound healing outcomes. Either directly through effects on cells involved in wound healing or indirectly through effects on systemic processes that can affect healing.[4] As a result, no clinical recommendations exist regarding the impact of diabetic medications on the healing of chronic wounds.[5]

Decreased insulin action is a hallmark of diabetes. Systemic insulin treatment is used for glycemic control, and according to the CDC, over 6 million Americans use insulin as a daily diabetes treatment. Insulin plays an important role in glucose metabolism, protein synthesis, and proliferation and differentiation of different cell types, suggesting that the hormone can affect various processes in wound healing.[4] Additionally, insulin has been shown to induce an anti-inflammatory effect in monocytes from obese patients via reduced NF-κB signaling and ROS generation. Despite the millions of patients taking insulin, no large prospective or retrospective clinical trials have been performed on the effects of systemic insulin treatment on the incidence or healing of diabetic chronic wounds. However, several

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studies, including small clinical trials, have shown that topical insulin application improves wound healing in diabetic humans and animals.[6-7]
Hence the present study was carried out to perform the comparative evaluation of insulin with an oral anti-diabetic drug in type 2 diabetic wound healing.

MATERIALS AND METHODS

This prospective observational study was conducted from September 2021 to December 2022 in Govt Tiruvannamalai Medical College, Tamil Nadu. A total of 224 patients having diabetic ulcer feet were selected, and written consent and Institutional ethical committee approval were taken before the start of the study.
Inclusion criteria: Patients of either sex with Type II Diabetes are between 40 and 65 years. Patient with normal range of hemoglobulin, lipid profile, liver function test (LFT), renal function test (RFT), and BMI. Patients with a wound on the plantar and dorsum of the foot and having Wagners classification of diabetic wound grade 1 and 2. Wounds of less than two months on the plantar aspect and less than one month on the dorsum of the foot were selected (Table 1).
Exclusion criteria: Patients with Type 1 diabetes and Wagner's classification 3 to 5. Patient with cardiac, renal, thyroid and anaemia and wound sepsis. Patients aged less than 40 and more than 65 years were excluded.
All 224 subjects were divided into two groups, namely Group I comprising 124 patients on Insulin therapy and Group II, having 100 patients treated with an oral hypoglycaemic agent (OHA). Patients in Group I was treated with insulin, i.e. Human mixtard 50/50 (40 IU injection) or Human mixtard 30/70 (100IU/ml), whereas patients in Group II were given OHA, i.e. Glimepirides, Gliptins, Metformin. After the therapy for two weeks, the mean ulceration area was observed for both patients, and a comparative evaluation was don.

Table 1: Wagner's grading

Grade 0	Intact Skin but high-risk foot
Grade 1	Superficial Ulcer
Grade 2	Deep ulcer with no abscess, no osteomyelitis
Grade 3	Ulcer with abscess, with osteomyelitis
Grade 4	Forefoot gangrene
Grade 5	Full foot gangrene

The distribution of age and gender was expressed as proportions. The selection was made using Wagner's grading, and the chi-square test did wound assessment between two groups. The comparison of the effectiveness of each group was assessed using length, breath and area reduction on day 1, day seven and day 15 using an independent t-test. Lab investigations such as Hemoglobulin, HBA1C, and wound swabs were also assessed using an independent T-test. A p-value of less than 0.05 will be considered statistically significant.

RESULTS

In the present study, 224 patients, in Wagner's classifications 1 and 2, aged more than 40 and less than 65 years having diabetic ulcer foot, were enrolled for the study. Maximum patients 105 (46.87%) were reported in the age group of 56 to 60. Most patients were male in Group I (62.9%) and Group II (62%). The initial size of the ulcer was recorded in both groups of patients. The maximum ulcer size of 5-10 cm2 was recorded in most patients in both groups (Group I: 54; Group II: 38) [Table 1].

Table 2: Distribution of age in both groups

		Both Group I, II
Age group (Years)	41 - 45	3
	46 - 50	10
	51- 55	58
	56- 60	105
	61- 65	48

In our study, both group patients showed a decrease in the mean size of a wound after 2-week treatment. Patients of Group II treated with insulin showed more decrease in mean wound ulcer size than Group I patients treated with OHA [Table 3].

Table 3: Distribution of patient characteristics

		Group I (Patient on insulin)	Group II Patient on OHA
Gender	Male	78	62
	Female	46	38
Maximum ulcer size in cm2	5-10 CM	54	38
	3-5 CM	26	28
	<3 CM	44	34
Mean ulcer area size in cm2	Initial size	21	20.7
	At the end of the first week	15.1	16.1
	At the end of the second week	8.2	11.2

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DISCUSSION

Diabetes Mellitus is usually associated with long-term complications, even if the blood sugar is maintained in the normal range. Foot ulcers following trauma, itching, and bite make the patient even to get hospitalized or may lead to lower extremity amputation.8 Regular dressing, diet, and blood sugar control improve wound healing. In this study, short-acting and intermediate-acting insulin combinations were used. Similarly, oral anti-diabetic drugs sulphonylureas, biguanides and dipeptidyl peptidase-4 are used in combination for diabetic control to maintain a sugar level of less than 200mg/dl.

In the present study, male predominance was reported in both groups. Zhang et al. also reported male predominance in their investigations.9 Maximum patients 105 (46.87%) were reported in the age group of 56 to 60. Vatankhah et al. reported a mean of patients 60 years in their study, similar to our study observations.10 The maximum ulcer size of 5-10 cm2 was recorded in the majority of patients in both Group I, 54(43.54%) and Group II, with 38(38%) patients. These findings in our study follow earlier reported studies.[11]

In this study between insulin and OHA on diabetic wound healing, a significant wound size reduction was observed (mean-35%) in insulin usage. The decrease in wound size in oral hypoglycaemic agent usage is lesser than insulin (mean-20%). The percentage of wound reduction between insulin and an oral hypoglycemic agent is $p<0.001$. In this study, insulin administration provides a favourable outcome by better reducing wound size in diabetic ulcers. Though OHA may increase insulin secretion, direct insulin administration improves wound healing. The requirement for insulin gets reduced as the wound granulates. Few patients in both groups experienced complications of Hypoglycaemia.

In a recent study, topical use of 0.5 units (U)/100-gram insulin cream on chronic wounds of patients with type 2 diabetes as part of a prospective, double-blind, randomized clinical trial showed complete wound closure in 4 out of 10 patients by eight weeks vs. none in the placebo group of 12 patients.[12] A pilot trial tested the angiogenic potential of insulin treatment on eight diabetic patients presenting with full-thickness wounds by treating half of their wounds topically with 10 U of insulin while leaving the other half untreated for 14 days. Their results indicated that biopsies from the insulin-treated half showed a higher number of new vessels (96 +/- 47) vs. the non-insulin side (32.88 +/- 45).[13]

Furthermore, in the outpatient clinical setting, topical application of 10 U of insulin on non-diabetic patients with acute (crush wounds, burns) and chronic wounds (pressure ulcers). This resulted in a faster daily rate of wound closure (46.09 mm2/day) compared to saline-treated patients (32.24 mm2/day). However, while the time to heal (45 days +/- 2 days) was not different between the two groups, the wound sizes in the insulin treatment group were larger at treatment initiation.[14]

CONCLUSION

In the present study, patients treated with insulin (Group I) showed better wound size healing improvement than those treated with OHA (Group II).

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