

Effect of Sildenafil in the Management of Grade 2 Diabetic Foot Ulcers: A Prospective Study

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Abstract

Background: Diabetes mellitus has become a global epidemic. Mortality and morbidity due to this is increasing in alarming proportion. The financial burden to society by this is markedly increasing every year.

Materials and Methods: This randomized control study included 72 patients of age group 44–75 (36 studies and 36 control groups). The study group is provided sildenafil 25 mg daily orally for 36 days. The phase of the healing process is compared in both groups.

Results: In the study group, all 36 patients showed complete healing in 22 days but in control group, only 6 patients had complete healing on 36 days and other 30 patients are at various stage of healing. The difference was obvious statistically.

Conclusion: Although the sildenafil is mainly used for erectile dysfunction syndrome and other medical conditions its role in the management of diabetic foot ulcer is commendable.

Key words: Diabetic foot ulcers, Sildenafil, Wound healing

INTRODUCTION

Diabetic mellitus has become a global epidemic with 387 million people harboring this problem. In India, 65 million people live with diabetic mellitus in the age group of 20–74 years.^[1] Diabetic foot ulcers (DFU) is one of the lethal complications of untreated patients which is gradually increasing in the Indian sub-continent.^[2] In the global scenario, one limb being lost in every 20 s. 10–15% of diabetic patients develop DFU mainly due to neuropathy, foot deformity, and ischemia.^[3]

Multiple organ involvement in DM increases the morbidity and mortality if the glycemic profile is not maintained to normal values. Atherosclerosis, peripheral neuropathy, ischemia, low immune status, and high blood sugar level

predisposes the lower limb especially foot to ulcerate. Negligence leads to many of DFU. According to Wagner classification, diabetic foot is graded according to the intensity of pathology (six grades).

- Grade-0 At risk foot
- Grade-1 Superficial ulcer, not clinically infected
- Grade-2 Deep ulcer, often infected no bone involvement
- Grade-3 Deep ulcer, abscess formation, bone involvement
- Grade-4 Localized gangrene (toe or forefoot)
- Grade-5 Gangrene of whole foot.

Management of diabetic foot involves local and systemic measures. It needs judicious use of antidiabetic drugs, antibiotics, vasodilators, statins, platelets agglutination inhibiting drugs, and surgical toilet. Topical application of platelet-derived growth factor and granulocyte macrophage-colony stimulatory factors (GM-CSF) were tried but with limited success.^[4] Many novel approaches to DFU are advocated in this decade such as bioengineered skin and tissue equivalent, negative pressure therapy,^[5] hyperbaric oxygen therapy,^[6-10] electrical stimulation,^[11] ultrasound therapy,^[12] and stem cell therapy^[13] but the results are highly variable.

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Proper meticulous cleaning of ulcer floor with copious flow of normal saline after desloughing is very important so as protection of the wound from environmental contamination. Sildenafil a phosphodiesterase inhibitors used widely for erectile dysfunction syndrome and pulmonary hypertension.^[14] It dilates the vasculature by preventing the inactivation of cyclic guanosine monophosphate (GMP). Accumulation of cyclic GMP produces good vasodilation. Sildenafil is contraindicated in patients on vasodilators for coronary artery disease as this may lead to alarming hypotension.^[15] Toxicity of this drug may be enhanced by taking drug such as macrolide antibiotics, imidazole, statins, and antiretroviral agents.

The principle behind the rationale is its vasodilator effect; hence, ulcer bed gets more blood and healing will be faster. Its effect on endothelium is reported by few authors prompted us to conduct this study.^[16] All patient in the study group is given 25 mg of sildenafil for 36 days (study period).

MATERIALS AND METHODS

A total of 72 patients were selected for this study [Table 1]. The study period was from 2013 to 2015 from a single institution. Patients were divided into two groups of 36 – one being the study group and other the control group. All the patients were given routine management including desloughing, antibiotics according to the culture study, rapid insulin (soluble), B complex factors and good nutrition.

Selection Criteria

- Age group 45–70 years.
- Patient with severe coronary artery disease, chronic renal disease, and peripheral vascular disease with severe ischemia was excluded from the study.
- Diabetic foot with only Grade II is selected for the study.

Patients history, clinical examination with sex and age, duration of disease, treatment taken in the past, vascular and neurological factors, and disabilities are recorded. The average measurement of ulcer is done at the beginning of the study and is made into three categories of ulcer 10 cm², 7 cm², and 5 cm², respectively. All the ulcers cleaned with normal saline irrigation and measurement is taken by tracing the outline on the butter paper and is transferred on graph paper. Figure 1 depicts first day of study. The procedure was done on beginning 8th, 15th, 22nd, 29th, and 36th days, respectively. Reduction in serous discharge and rate of granulation tissue presence and reduction in ulcer margin was meticulously recorded on the 8th day of the study. 20 (55.5%) case showed pale granulation tissue 14 (38.8%)

good granulation tissue and 2 (5.5%) case partially healed, whereas in control group 24 (66.6%) cases showed no change in ulcer floor 6 (16.6%) cases showed pale granulation tissue and another 6 (17%) showed good granulation tissue [Figure 2]. Even after 8 days, the improvement in the study group is remarkable. On the 15th day, 14 (38.8%) cases with pale granulation tissue and 16 (44.4%) cases with good granulation tissue and 2 (5.5%) cases completely healed in the study group whereas in control group 8 (22.2%) cases showed no change, 16 (44.4%) case with pale granulation tissue, 10 (27.7%) cases with good granulation tissue, and 2 (5.5%) cases partially healed [Figure 3]. After 3 weeks (on day 21) study group showed all 36 (100%) cases completely healed, whereas in control group 10 (27.7%) cases showed pale granulation tissue, 20 (55.5%) cases good granulation tissue, 2 (5.5%) cases partially healed, and 4 (11%) cases completely healed [Figure 4]. On the 29th day, control

Table 1: Distribution of cases according to age and sex

Age group	Male (%) n-40	Female (%) n-32	Total n-72
44–55	8 (20)	6 (18.75)	14 (19.4)
56–65	14 (35)	14 (43.75)	28 (38.8)
66–75	18 (45)	12 (37.5)	30 (41.6)
Total	40	32	72

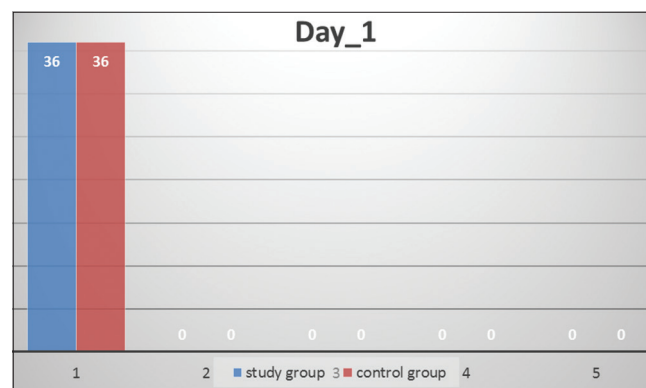


Figure 1: Bar diagram Day 1

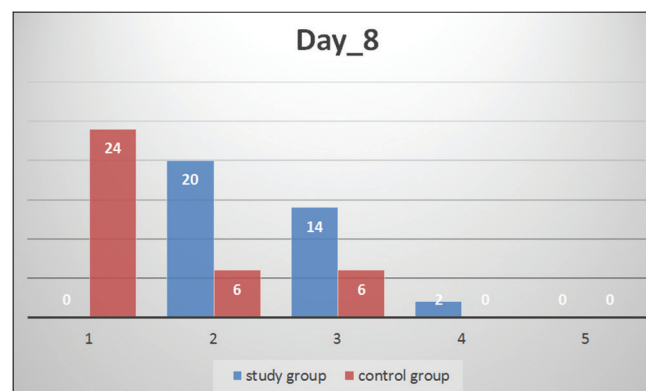


Figure 2: Bar diagram showing result on Day 8

group showed 8 (22.2%) case with pale granulation tissue, 12 (33.3%) cases with good granulation tissue, 10 (27.7%) with partial healing, and 6 (16.6%) cases with complete heal [Figure 5].

At the end of evaluation (36th day) control group showed 14 (38.8%) cases completely healed whereas 8 (22.2%) cases having only good granulation tissue [Figure 6]. The difference was found to be statistically significant [Table 2].

DISCUSSION

Diabetic mellitus is a systemic disease involving all organs in the human body leading to a grave situation if the glycemic profile is not controlled properly. The morbidity related to a complication of diabetes mellitus (DM) in gradually increasing in urban, semi-urban, and rural population during the past few decades according to the studies done in the past by many authorities. DFU is one of the most common surgical complications of DM in the surgical outpatient department in our hospital.

In DFU healing is by secondary intention by granulation, contraction, and epithelialization. There is increased

inflammation and proliferation.^[17] Prolonged inflammatory phase leads to overgrowth of tissue and heals by scarring. Here, the role of fibroblasts, platelets-derived growth factor, GM-CSF, insulin-like growth factors, transforming growth factors (TGF)- β , and TGF- α is highly involved.

In the management of diabetic wound, two things are very important. It includes providing more blood to the affected area and wound care. Here, the blood supply to the lower limb is highly compromised due to progressing atherosclerosis. Our aim is to enhance the perfusion in the affected part so that the concerned growth factor and other anti-inflammatory

Table 2: comparative analysis of study and control groups

Duration	Outcome of patient analysis									
	Study group					control group				
Days	1	2	3	4	5	1	2	3	4	5
1	36	0	0	0	0	36	0	0	0	0
8	0	20	14	2	0	24	6	6	0	0
15	0	14	16	4	2	8	16	10	2	0
22	0	0	0	0	36	0	10	20	2	4
29	0	0	0	0	0	0	8	12	10	6
36	0	0	0	0	0	0	0	8	14	14

1. Granulation tissue absent, 2. Granulation tissue pale, 3. Granulation tissue good, 4. Partially healed, 5. Completely healed

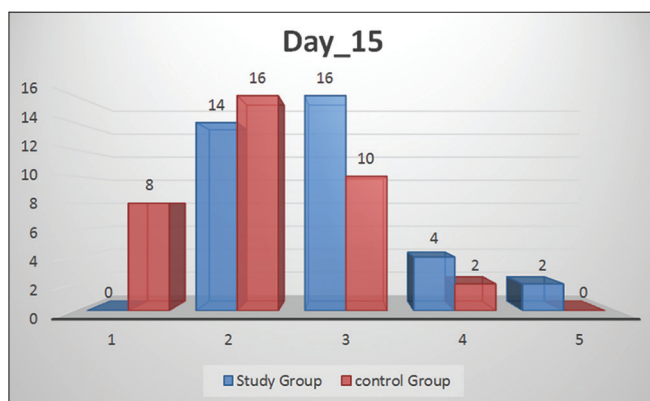


Figure 3: Bar diagram showing result on Day 15

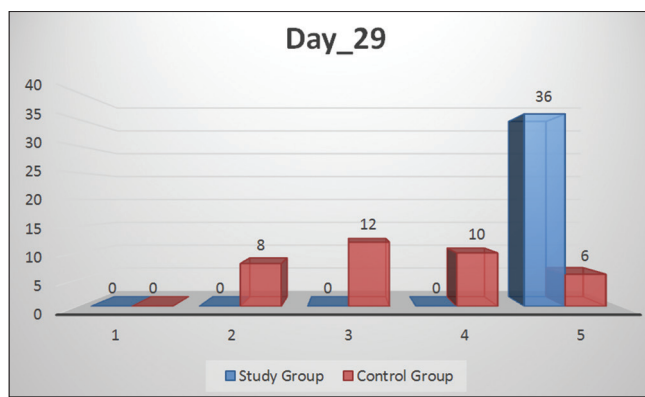


Figure 5: Bar diagram showing result on Day 29

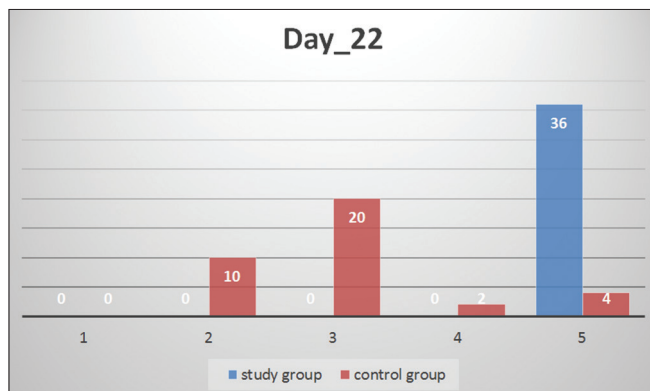


Figure 4: Bar diagram showing result on Day 22

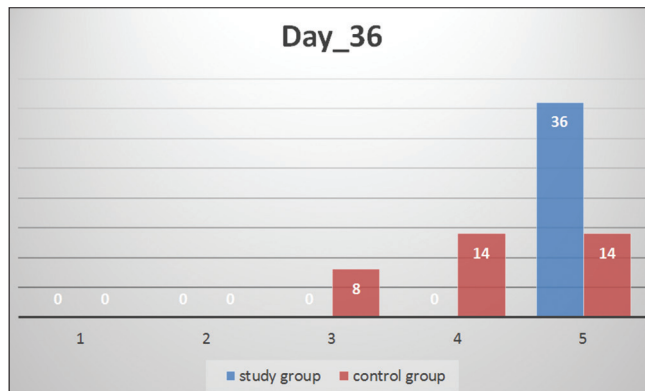


Figure 6: Bar diagram showing result on Day 36

mediators reach the wound site. Blood supply can be enhanced by many modalities such as dilating the lumen of arteries and decreasing the viscosity of blood, increase microcirculation, increase the flexibility of RBC; hence, it can go through the capillaries to provide more oxygen to the tissue. Drugs such as pentoxifylline (trental) and cilostazol are used for dilating the vessels aspirin used to prevent clumping of platelet, statins to control the atherogenesis.

In our study, sildenafil was given 25 mg/day for 36 days. It is a potent vasodilator. The study report is encouraging. Healing is very fast compared to the control group. Hence, apart from good wound care, providing more blood supply to the wound site is very important.

CONCLUSION

Meticulous wound care with supplementation of sildenafil in DFU Grade II makes the wound reduction rate faster in comparison with wound care alone. The role of this phosphodiesterase inhibitors in the DFU management will be a boon to the diabetic patient. Our study is only limited to a small number of the patient; hence, study involving a large segment of the population with sildenafil is essential for further evaluation.

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