Original Article

A prospective, randomized, controlled trial of autologous platelet - rich plasma for the treatment of diabetic foot ulcers

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Abstract

Objective: To evaluate the safety and efficacy of autologous platelet-rich plasma for the treatment of nonhealing diabetic foot ulcers. **Methods:** Type of study – Prospective Randomized Controlled Blinded clinical study. Sample size – 50. The patients admitted with diabetic foot ulcer in surgery wards in Vinayaka Missions Medical College and Hospital, Karaikal. **Inclusion criteria:** Persons with type 2 diabetes. Age more than 18 years. Ulcer of at least 4 weeks' duration. Hba1c < 8. Foot ulcer located on the plantar, medial, or lateral aspect of the foot. Wound measurement between 3 cm and 5 cm. Post debridement, the ulcer should be comprised of healthy vascularized tissue and free of necrotic debris, foreign bodies, sinus tracts, tunneling, and undermining and at least 4 cm from any additional wound. Limb with adequate perfusion. **Exclusion criteria**: Ulcer due to non-diabetic etiology. Evidence of gangrene in ulcer or on any part of the foot. Patients undergoing renal dialysis, known immune insufficiency, known abnormal platelet activation disorders, liver disease, active cancer (except remote basal cell of the skin), malnutrition, hematologic, collagen vascular disease, rheumatic disease, or bleeding disorders. Women of childbearing age excluding pregnant or lactating. **Conclusion:** It was observed that postmenopausal women with thyroid dysfunction, especially subclinical hypothyroidism, had lipid abnormalities. Lipid abnormalities seen in subclinical hypothyroidism patients are mainly in the form of significant elevation of total cholesterol and HDL. According to this study, thyroid dysfunction is directly related to total cholesterol and HDL changes ($p< 0.01$).Changes have also been noted with thyroid dysfunction and Non HDL Cholesterol mainly LDL and VLDL but, they were not statistically significant. Therefore, in post menopausal women with thyroid dysfunction evaluation of lipid profile should me made mandatory to avoid the risk of Coronary artery disease, Cerebrovascular accident.

Key Word: autologous, platelet rich plasma, diabetic foot.

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INTRODUCTION

Diabetes mellitus is a metabolic diseases characterized by hyperglycemia. It results from defects in insulin secretion, insulin action or both. Diabetes is rapidly increasing and emerging as a global epidemic. Chronic hyperglycemia is results in long-term damage, dysfunction, and failure of various organs, including the eyes, blood vessels, kidneys, heart, etc. Diabetes can be broadly divided into Type 1 and Type 2. Type 1 diabetes due to absolute deficiency of insulin secretion and Type 2 due to combination of resistance to insulin action and an inadequate compensatory insulin secretory response. Diabetic foot is one of the major complications of diabetes, with increased chance of infection, ulceration and neurological abnormality. Results in worldwide medical, social and economic burden. Autologous platelet-rich plasma (PRP) is rich in growth factors. Use of this minimally invasive technique bears similarity to natural wound healing process. It hastens wound healing. Platelet-rich plasma is a novel treatment.

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Need for study:

Traditional or conventional treatments for diabetic foot are costly and require long periods of hospitalization. This results in a huge economic burden to patient family and society. Growth factors in platelet rich plasma modulates cell proliferation and synthesis of extra cellular matrix. Being autologous its safe and cost-effective method of wound healing.

METHODOLOGY

Material and Methods

- Project was submitted to ethical committee, got approval from the ethical committee. Test and control population were recruited after obtaining all necessary consent in their local/regional language.
- All the patients admitted with diabetic foot ulcer in surgery wards in Vinayaka Missions Medical College and Hospital, Karaikal were included in study.

Method Of Collection Of Data And Method Of Study

- The purpose of the study was explained to the patient and consent obtained.
- Patients were recruited as per inclusion-exclusion criteria.
- Relevant history including symptoms and signs, past medical history, drug history and examination findings noted. Data was collected using a proforma meeting the objectives of the study.

RESULTS AND DISCUSSION

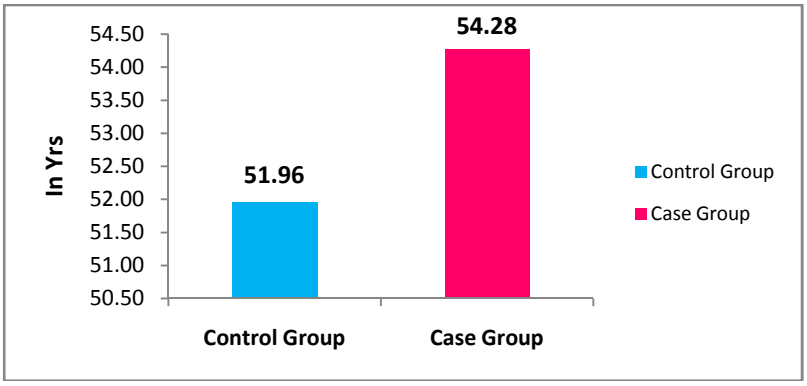
Demographic Data

In this study, 50 patients who fulfilled the inclusion-exclusion criteria were selected. Out of which, 25 were chosen as study/test group and 25 as control group.

Subjects with age more than 18 years were included in the study. Age distribution in test and control group were evaluated and it was found that mean age in test group was 54.28years with standard deviation of 8.54.Whereas in control group mean age was 51.96 and standard deviation was 11.39.But difference between two groups was not statistically significant.

Table 1: Age distribution of test and controls

	Control Group			Test Group			
Variable	N	Mean	Std. Dev.	N	Mean	Std. Dev.	P Value
Age	25	51.96	11.39	25	54.28	8.54	>0.05



Graph 1: Showing the age distribution of test and controls

Distribution of cases and controls

Out of 50 study subjects, 25 were chosen as test group who were treated with platelet rich plasma and remaining 25 as control group treated with saline dressing.

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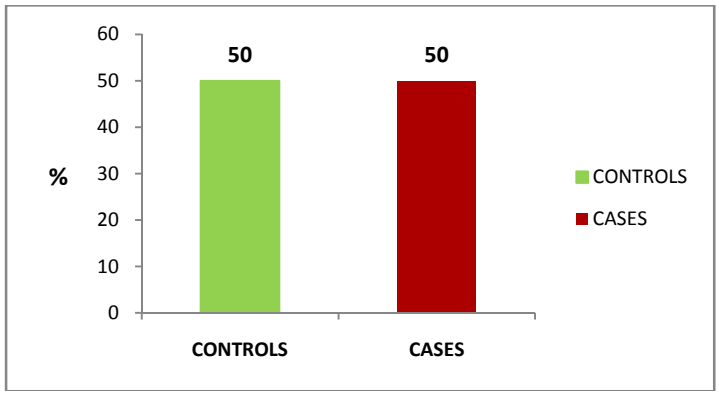
Table 2: Distribution of cases and controls

GROUP	N	Percent
Controls	25	50
Test	25	50
Total	**50**	**100**



Graph 2: Distribution of cases and controls

Comparison of glycaemic parameters

Glycaemic parameters like fasting blood sugar, post prandial blood sugar and HbA1c of test and control group were evaluated**.** On comparison of fasting blood sugar values, this study showed that mean fasting blood sugar was 99.68 among test group and 98.20 among controls. The difference was not found to be statistically significant

Table 3: Comparison of fasting blood sugar values

	Control Group			Test Group			
Variable	N	Mean	Std. Dev.	N	Mean	Std. Dev.	P Value
FBS	25	98.20	17.96	25	99.68	17.17	>0.05

Post prandial blood sugar values

Post prandial blood sugar values among test and control groups were evaluated and it was found that mean was 125.72 in test subjects in comparison to 125.56 in controls. The difference was not statistically significant

Table 4: Comparison of post prandial blood sugar values

	Control Group			Test Group			
Variable	N	Mean	Std. Dev.	N	Mean	Std. Dev.	P Value
PPBS	25	125.56	17.17	25	125.72	15.99	>0.05

Comparison of HbA1c values

HbA1c values of test and control groups were evaluated. It showed that mean HbA1c in test group was 6.05 with standard deviation of 0.56, whereas in control group mean was 6.06 and standard deviation 0.50.But the difference was not statistically significant

Table 5: Comparison of HbA1c values

	Control Group			Test Group			
Variable	N	Mean	Std. Dev.	N	Mean	Std. Dev.	P Value
HbA1C	25	6.06	0.50	25	6.05	0.56	>0.05

Comparison of ulcer size between test and controls

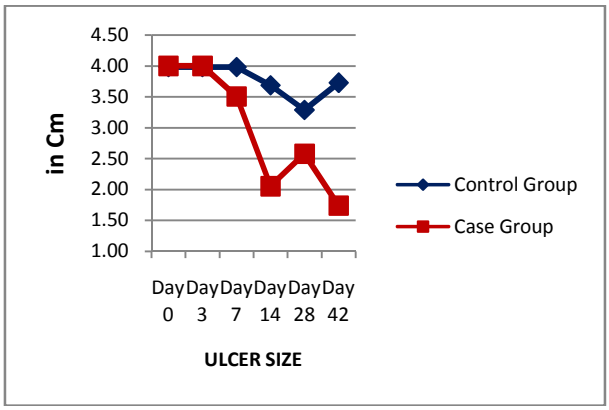
In this study, ulcer size was measured on days 3, 7, 14, 28 and 42.Mean ulcer size at each visit was calculated for test and control group. It was found that test group had decrease in ulcer size, indicating better healing compared to control group on all these days.

Table 6: Comparison of ulcer size

	Control Group			Test Group			
Ulcer Size (in Cm)	N	Mean	Std. Dev.	N	Mean	Std. Dev.	P Value
Day 0	25	3.98	0.68	25	4.00	0.59	>0.05
Day 3	25	3.98	0.68	25	4.00	0.59	>0.05
Day 7	25	3.98	0.68	25	3.50	0.60	<0.05
Day 14	25	3.69	0.99	22	2.05	1.22	<0.01
Day 28	25	3.29	1.49	10	2.58	0.84	>0.05
Day 42	20	3.73	1.12	10	1.74	1.22	<0.01

Table 6 shows the change in mean ulcer size. There is no statistical difference in mean ulcer size in Day 0, 3 and 28, whereas there is a statistical difference in mean ulcer size comparing case and controls in Days 7, 14 and 42.

And in all these days 7, 14 and 42, the Test group had better wound healing compared to the control group.



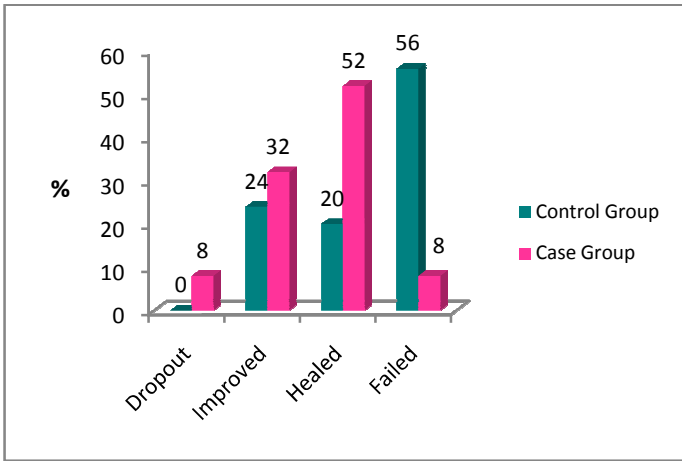
Graph 3: Comparison of ulcer size

Final assessment of wound healing in test and control

This study showed that in the test group who received platelet rich plasma therapy, complete healing was seen in 52% of the cases by the end of 28 days, where as improvement was seen in 32% of the cases. There was a 8% dropout and the rest 8% showed no improvement. In control group only 20% showed complete healing by the end of 42 days, improvement seen only in 24% of the cases. While there were no dropouts in the control group, 56% of the cases showed no improvement.

Table 7: Final assessment of wound healing

	Control Group		Test Group	
FINAL ASSESSMENT	N	Percent	N	Percent
Dropout	0	0	2	8
Improved	6	24	8	32
Healed	5	20	13	52
Failed	14	56	2	8
Total	**25**	**100**	**25**	**100**



Graph 4: Final assessment of wound healing

DISCUSSION

Chronicity in foot ulcers

Diabetic foot ulcers are classified as acute or chronic according to their duration; however, there is no consensus as to a specific length of time to define chronicity. An acute ulcer usually should heal in less than a month. Among chronic ulcers, duration of 6 months or more seems to define the most recalcitrant ulcers.[5]

Diabetic Foot Ulcer

Among diabetic patients, 2-3% will develop a foot ulcer each year, 15% will develop a foot ulcer during their lifetime.[7] Although the pathogenesis of peripheral sensory neuropathy is still poorly understood, there seem to be multiple mechanisms involved, including the formation of advanced glycosylated end products and diacylglycerol and oxidative stress.[8]

Healing Of Foot Ulcers

The frequency and severity of wound infection is increased in diabetes, which may be related to high glucose levels or impairment of granulocytic function and chemotaxis.[9] In addition, there seems to be a prolonged inflammation, impaired neovascularisation, decreased synthesis of collagen, an abnormal pattern of synthesis of extracellular matrix proteins and decreased fibroblast proliferation.[10]

Autologous Platelet Rich Plasma

Autologous Platelet Rich Plasma is a cost-effective method of wound healing. It enhances wound healing by promoting the healing process by growth factors present in it. They are platelet-derived growth factor (PDGF-αα, αβ, αβ), fibroblast growth factor, vascular endothelial growth factor, epidermal growth factor and transforming growth factor. These growth factors are important in modulating mesenchymal cell recruitment, proliferation and extra-cellular matrix synthesis during the healing process.

Platelet Derived Growth Factors

Platelet Derived Growth Factors stimulate chemotaxis, proliferation and new gene expression in monocytes, macrophages and fibroblasts *in vitro*, cell types considered essential for tissue repair. Transforming growth factor-β stimulates cell proliferation, protein synthesis and collagen synthesis. It also inhibits growth of many epithelial tumour cells and fibroblastic cell lines.

Mechanism Of Action Of Growth Factors

Platelet-derived angiogenesis factor is a polypeptide capable of stimulating new capillary growth by inducing migration of endothelial cells. Platelet-derived epithelial cell growth factor is partially responsible for the initial influx of neutrophils into the wound space; it is also a mitogen for many cells, including epithelial cells and fibroblasts. More recently, it was suggested that this was the mechanism by which platelet factors influence the

process of angiogenesis and revascularisation, thus promoting granulation tissue formation. The aim of this study was to evaluate the safety and efficacy of autologous platelet-rich plasma for the treatment of nonhealing diabetic foot ulcers. In this study, the effect of platelet-rich plasma was compared with that of normal saline dressing, by recruiting 50 patients, who were subjected to either platelet-rich plasma injection or normal saline dressing using a prospective, randomized, controlled and blinded study approach.

Demographic Data

Gender distribution

This study consisted of 50 patients with diabetic foot ulcer who fulfilled the inclusion and exclusion criteria of whom 60 % (30 cases) were females and 40 % (20 cases) were males.

Age distribution

The mean age distribution for cases and control were 51.96 yrs in control group and 54.28 yrs in case group. The difference in age wasn't statistically significant.

Glycaemic Parameters

Mean fasting blood sugar

The mean fasting blood sugar level was compared between the control and case group which showed the mean fasting blood sugar level was is 98.2 mg/dl in control group and 99.68 mg/dl in case group. Hence there was no statistically significant difference in the fasting blood sugar levels between the cases and control.

Mean post prandial blood sugar

The post prandial blood sugar level was compared between the control and case group which showed the mean post prandial blood sugar is 125.56 mg/dl in control group and 125.72 mg/dl in case group. Hence there was no statistically significant difference in the post prandial blood sugar levels between the cases and control.

Mean HbA1C levels

The HbA1C levels was also compared between the control and case group which showed the mean HbA1C is 6.06 in control group whereas 6.05 in case group. Hence there was no statistically significant difference in the HbA1C levels between the cases and control.

Change in Ulcer Size

Finally the wound size was measured and compared on day 0, day 3, day 7, day 14, day 28 and day 42 for all patients included in this study. It was observed that there was no difference in mean ulcer size in Day 0, 3 and 28, whereas there was a difference in mean ulcer size comparing case and controls on Days 7, 14 and 42 and in all these days 7, 14 and 42, the test group had better wound healing when compared to the control group.

FINAL ASSESSMENT OF WOUND HEALING

Wound Healing In Test Group

This study showed that in the test group who received platelet rich plasma therapy, complete healing was seen in 52% of the cases by the end of 28 days, where as improvement was seen in 32% of the cases. There was a 8% dropout and the rest 8% showed no improvement.

Wound Healing In Control Group

This on comparison with the control group showed that in the control group only 20% showed complete healing by the end of 42 days, improvement seen only in 24% of the cases. While there were no dropouts in the control group, 56% of the cases showed no improvement in the ulcer size.

CONCLUSION

Level of healing

The study group results indicate an excellent reduction in ulcer size and the percentage of subjects who were completely healed (52%), as compared to control subjects treated with saline (20%). Improvement was seen in 32% of the cases as compared to 24% in control group.All cases in test group were either completely or partially healed,while 56% of subjects in control group were not healed at all.

Rate of healing

Further, the rate of healing was so remarkable, in fact fifty-two percent of study patients were healed by 28 days itself. While even twenty percent of patients who were healed in control group, took twice the time to heal , that is, 42 days. However, the dropout rate was 8% in study group. In these dropout patients ,on the fourteenth day, wound was healing very well and was probably completely healed by 28 days .The dropout was because , subjects did not feel the need to come to hospital as they were healed.

Moreover, in 56% of controls there was no improvement at all in ulcer size. But there were no dropouts in this group in spite of no improvement.

Correlation with Glycaemic status

It was also observed that the glycaemic state of the test subjects and glycaemic state of control subjects was the same, as seen by the lack of difference in glycaemic state of both groups. This indicated that ulcer healing was not sequalae to improvement in diabetic status, but because of the superior efficacy of the platelet rich plasma therapy.

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