

A COMPARATIVE ANALYSIS OF THE MERITS OF TOPICAL PLACENTAL EXTRACT OVER CONVENTIONAL METHODS OF DRESSINGS FOR DIABETIC FOOT ULCERS

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ABSTRACT

BACKGROUND

Foot ulceration is thought to affect 15% of people with diabetes at some time in their lives. This is because of complex association of various factors like - Ischaemia, Neuropathy and Infection.

MATERIALS AND METHODS

The patients selected had ulcers in their foot secondary to trauma or had spontaneously developed the ulcer. Recruited patients were randomised to receive either topical application of human Placental Purified Extract (PPE) on the debrided wounds (Group P) or were debrided and dressed with diluted povidone iodine initially till the infection cleared and then with simple saline (Group C). A total of 100 patients were included in the study. Group P had 35 males and 15 females and Group C had 37 males and 13 females.

Statistical Analysis - Continuous variables were assessed with Wilcoxon Signed Rank Test and Student's t-test. An intention to treat analysis was done and the value of significance was considered as < 0.05.

RESULTS

Average area of the wound in Group C at the time of admission was 79.16 cm² and at the time of discharge the wound had contracted on an average to an area of 65.43 cm², in Group P average area of the wound at the time of admission was 72.78 cm² and at the time of discharge the wound had contracted on an average to an area of 52.55 cm², which is statistically significant. After dressing the wound, average time for complete granulation was 14.98 days in Group P, while 20.14 days in Group C. Rate of Wound Contraction in Group P was 27.7% and in Group C was 17.3% which is significant.

CONCLUSION

Surgical debridement is the cornerstone of management of diabetic foot ulcers. Purified placental extract dressings showed faster and better healing rates when compared with conventional dressings.

KEYWORDS

Purified Placental Extract, Diabetic Foot Ulcer.

HOW TO CITE THIS ARTICLE: Vardhan VJP, Nagateja MV. A comparative analysis of the merits of topical placental extract over conventional methods of dressings for diabetic foot ulcers. J. Evolution Med. Dent. Sci. 2017;6(12):963-966, DOI: 10.14260/jemds/2017/206

BACKGROUND

Diabetes Mellitus (DM) is a chronic disorder of glucose metabolism with multisystem involvement and serious long-term consequences. However, globally there is a notable increase in the incidence of DM and this trend is closely linked to population growth, urbanisation, obesity and physical activity. By 2030, it is estimated that the number of diabetic people worldwide will increase from 382 million currently to 552 million.¹

Approximately, 9% of the Indian urban population and 3% of the rural population is estimated to have diabetes. Foot ulceration is thought to affect 15% of people with diabetes at some time in their lives.²

Financial or Other, Competing Interest: None.

Submission 30-12-2016, Peer Review 25-01-2017,

Acceptance 31-01-2017, Published 09-02-2017.

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DOI: 10.14260/jemds/2017/206



This is because of complex association of various factors like - Ischaemia, Neuropathy and Infection. Microangiopathy, hypercoagulable status, atherosclerosis and hyperglycaemia may lead to the above complex, thus leading to diabetic lesion and its complications.^{3,4,5} People with diabetes are between 15 and 70 times more likely to undergo lower limb amputations than people without diabetes.⁶

Adequate debridement must always precede the application of topical wound healing agents, dressings or wound closure procedures.^{7,8} Many techniques are available for wound dressing and all essentially reduce infection and improve granulation growth.

Placental extract increases collagen synthesis, increases tissue protein, accelerates neoangiogenesis and epithelialisation; has immunotropic effect, EGF (Epidermal Growth Factor) and Fibroblast growth factor. It supports ossification and reduces surrounding tissue inflammation and oedema.^{9,10,11} Studies have shown that use of topical placental extract increases the rate of wound healing due to the presence of amino acids, vitamins, nucleotides in it and patients have an early recovery.

In this study, the wound healing potential of topical placental extract was evaluated and compared with conventional dressings.

Aims and Objectives

1. To compare the merits of topical placental extract over conventional dressing in diabetic foot ulcers.
2. To study the rate of wound healing in the two groups.

Patients and Methods

This study was carried out in the Department of General Surgery, PES Institute of Medical Sciences and Research, Kuppam, Andhra Pradesh from November 2013 to October 2015. This is an observational study and the data was collected prospectively.

All diabetic patients with foot ulcers, who were admitted as in-patients, who gave consent, meeting the inclusion criteria were enrolled in the study. Patient’s history, clinical, biochemical and radiological data were collected.

Inclusion Criteria

- Type 1 and 2 diabetes mellitus.
- Diabetics between 18 - 75 years of age.
- Size of the ulcer less than 15 × 15 cm.
- Grade 1, 2 and 3 (according to Wagner classification - Table 1).

Exclusion Criteria

- Patients treated on OPD basis.
- Tissue hypoxia (ischaemia, venous insufficiency), absent - dorsalis pedis, anterior and posterior tibial, and popliteal artery pulse.
- Grade 4 and 5 wounds (According to Wagner classification - Table 1).
- Patients with diabetic ketoacidosis.

The patients selected had ulcers in their foot secondary to trauma or had spontaneously developed the ulcer. Recruited patients were randomised to receive either topical application of human placental purified extract (PPE/placentrex) on the debrided wounds (Group P) or were debrided and dressed with dilute povidone iodine initially till the infection cleared and then with simple saline (Group C).

Grade	Lesion
0	No open lesions: may have deformity or cellulitis
1	Superficial ulcer
2	Deep ulcer to tendon or joint capsule
3	Deep ulcer with abscess, osteomyelitis or joint sepsis
4	Local gangrene - forefoot or heel
5	Gangrene of entire foot

Table 1. Wagner Classification System

All patients were started on prophylactic antibiotics initially followed by targeted antibiotics according to culture sensitivity reports, long/short acting insulin for DM and analgesics/anti-inflammatory drugs.

In the present study, all patient’s glycaemic status was evaluated and were started on insulin according to sliding scale, initially followed by fixed doses when there was a good glycaemic control (long/short acting).

Continuous variables were assessed with Wilcoxon

Signed Rank Test and Student t-test. An intention to treat analysis was done and the value of significance was considered as < 0.05.

RESULTS

Observations

A total of 100 patients were included in the study. In that, the average age of patients in Group P was 55.7 years and in Group C was 57.9 years. Group P had 35 males and 15 females and Group C had 37 males and 13 females. Average duration of diabetes in Group P was 6.8 years and in Group C was 5.6 years. Mean HbA1c values of patients in Group C was 8.4% and in Group P was 8.3%; 73% of patients presented with ulcer secondary to trauma and in 27% of the patients the cause was unknown or had spontaneously occurred.

After dressing the wound, average time for complete granulation was 14.98 days in Group P, while 20.14 days in Group C. P value of this comparison was < 0.05 (0.0024), which is statistically significant suggesting better efficacy of placental extract dressing in diabetic wounds as compared to Group C.

Average area of the wound in Group C at the time of admission was 79.16 cm² and at the time of discharge the wound had contracted on an average to an area of 65.43 cm², in Group P average area of the wound at the time of admission was 72.78 cm² and at the time of discharge the wound had contracted on an average to an area of 52.55 cm² which is statistically significant.

In Group P - 88% of patients were treated conservatively and 12% had Split Skin Grafting (SSG); while in Group C 62% of patients were treated conservatively and 38% had SSG. Rate of Wound Contraction (% Reduction) in Group P was 27.7% and in Group C was 17.3% which is significant. The average hospital stay was 20 ± 1 days in Group P and 25 ± 1 days in Group C.

Purified placental extract (Placentrex) group had lesser hospital stay, lesser overall treatment time and faster wound healing.

DISCUSSION

Prevalence of diabetes in India is around 8%.¹² In a study conducted by Aziz et al who looked at predictive factors for lower extremity amputations, most patients are around 60 years with range from 21 - 91 years.¹³ In this study, 70% of the patients were over 50 years of age.

Lower Extremity Amputation (LEA) rate is 15 to 40 times higher in the diabetic patients.¹⁴ In 2002, the age-adjusted LEA rate among men was 7.0 per 1,000 persons with diabetes compared with the rate among women reported as 3.3 per 1000 persons with diabetes.¹⁵ In this study, men constituted more than 70% of the study population, probably due to more exposure to trauma.

Metabolic polyneuropathy predominantly affects the lower extremities.¹⁵ It is found in approximately 30% of diabetics and increases in prevalence with increasing duration of disease.¹⁶ Sensory involvement causes loss of sensation of pain and temperature, and subsequently perception of vibration. Because of this, diabetics are unable to detect changes in temperature, excess pressure produced by tight-fitting shoes or any other continued trauma. In this study 73% of the ulcers were traumatic in origin, trauma being the triggering factor secondary to neuropathy, 27%

were spontaneous in origin secondary to blister rupture or unnoticed trivial trauma.

The majority of wounds are caused by Staphylococcus aureus, beta-haemolytic streptococci and other gram-positive cocci.¹⁷

Patients who have been previously hospitalised with an open wound are more likely to develop an infection from resistant bacteria, such as methicillin-resistant S aureus (MRSA) and vancomycin-resistant enterococci (VRE).¹⁸ Chronic wounds may develop a more complex assortment of bacteria including gram-negative rods, obligate anaerobes, Pseudomonas aeruginosa and enterococci. Causative organisms are more reliably detected in specimens that are obtained deep rather than superficial swabs. The IDSA (Infectious Disease Society of America) formulated guidelines and key recommendations for treatment of DFU stating that an empirical antibiotic regimen should be implemented primarily on the basis of infection severity and likely pathologic agents.¹⁹ Optimally, definitive therapy should be based upon culture and susceptibility analysis.

In this study first line of empirical antibiotics used were metronidazole, cephalosporin (Preferably 3rd generation) and amikacin. Targeted antibiotics were administered based on culture and sensitivity report.

Many techniques are available for wound dressing. All reduce infection and improve granulation growth. Povidone Iodine is routinely used as antiseptic solution. It is used initially for discharging wound in presence of infection and then dressing done with normal saline. Normal saline covers up the wound and provides a moist environment for healing.

Placental extract is prepared from fresh term healthy human placenta after delivery; the amniotic membrane and cord are removed and HIV, HCV, HBsAg status checked. The tissue is then sterilised by two heat treatment steps - 90°C for 6 mins. and then at 121°C under pressure of 15 lbs for 40 mins. It is then preserved in gel form, each gram of which contains 0.1 g of fresh human placenta.^{9,10,20}

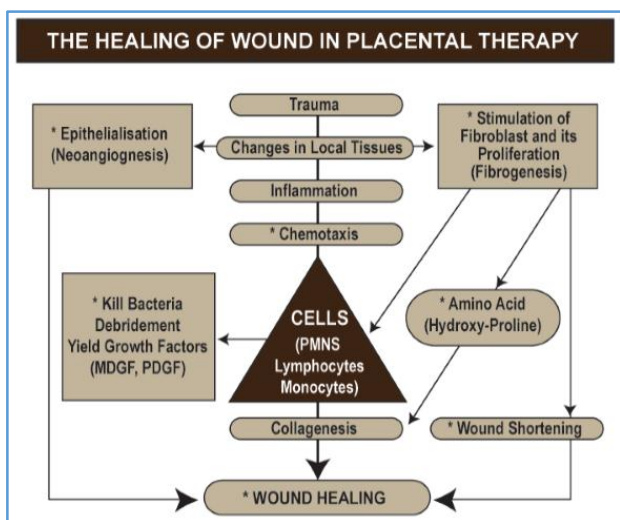


Figure 1. Cellular Mechanism of Repair in Placental Therapy

Chakraborty et al studied the role of placenta on the growth of different bacteria. They found that placenta prevents the growth of bacteria such as E. coli from urine and

blood culture. They found placenta to also have an inhibitory role in the growth of bacteria such as E. coli, Staphylococcus aureus and fungi such as Saccharomyces cerevisiae, Kluyveromyces fragilis and Candida albicans.²¹

Sudhir et al²² studied the effect of topical placental extract dressing over various diabetic ulcers and had similar results; 60 patients were included in the study and the patients were randomised into two groups consisting of 30 patients in each group. The results obtained are comparable to present study.

- Average age of the patients in both the groups were around 57 years, which was similar to the present study, where the average age is 56 years. Male-to-female ratio of 4:1 is noted in both groups in Sudhir et al study and in the present study male patients constituted about 70 percent of the study population.
- 35% of the patients presented had ulcer due to sensory loss, 30% - 35% with cellulitis/abscess and 15% with gangrene of toe or foot. In the present study 73% patients had an ulcer secondary to trauma and in 27% of the patients the cause of ulcer was unknown/spontaneously occurred.
- Average time for complete granulation of the wound was 14.2 ± 1 day in placentrex group, while 23.0 ± 1.4 day in the control group. In the present study, average time for complete granulation was 14.98 days in the placentrex group, 20.14 days in control group.
- The average hospital stay was 19.8 ± 2 day in placentrex group and 28.2 ± 2 day in control group. In the present study, the average hospital stay was 20 ± 1 day in placentrex group and 25 ± 1 day in the control group.

The reduction of pressure to the diabetic foot ulcer is essential to treatment.²³ Proper off-loading and pressure reduction prevents further trauma and promotes healing. Healed ulcers may be managed with shoes and variations of molded or multiple density insoles, while the total contact cast remains the standard approach to off-loading areas of ulceration. In the present study, patients with plantar ulcers were started on offloading foot wear and healed ulcers were started on multiple density insoles/custom molded foot wear.

Surgical management of diabetic foot ulcers is often required and includes aggressive incision, drainage and debridement of non-viable soft tissue and bone. Multiple debridements were necessitated among 1/3rd of the study population for the management of the diabetic foot ulcer.



Figure 2. Ulcer Healing with Conventional Dressings

Photographs taken on 14th day.



Figure 3. Ulcer Healing with Placentrex Application

Photographs taken on 14th day.

CONCLUSION

Surgical debridement is the cornerstone of management of diabetic foot ulcers, all patients underwent surgical debridement first followed by daily dressings with topical agents. Purified placental extract dressings showed faster and better healing rates when compared with conventional dressings. Wound granulated faster in the study group. The final area and percentage reduction of the wound was better in placentrex group. There were no adverse effects or reactions noted in any of the patients when Placentrex gel was applied over the ulcer.

Very few studies have been done to test the efficacy of purified placental extract on foot ulcers; needs studies with larger study groups to test efficacy of placentrex on various wounds.

REFERENCES

- [1] Shaw JE, Sicree RA, Zimet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010;87(1):4-14.
- [2] Spencer S. Pressure relieving interventions for preventing and treating diabetic foot ulcers. *Cochrane Database of Systematic Reviews* 2000;3:CD002302.
- [3] Rathur HM, Boulton AJ. Recent advances in the diagnosis and management of diabetic neuropathy. *J Bone Joint Surg* 2005;87(12):1605-10.
- [4] Glynn JR, Carr EK, Jeffcoate WF. Foot ulcer in previously undiagnosed diabetes mellitus. *British medical journal* 1990;300(6731):1046-7.
- [5] Singer AJ, Clark RA. Cutaneous wound healing. *N Engl J Med* 1999;341(10):738-46.
- [6] Campbell IW, Nairn M. Scottish intercollegiate guidelines network: management of diabetic (SIGN 55). *The British Journal Of Diabetes And Vascular Disease* 2002;2(1):50-2.
- [7] American Diabetes Association. Consensus development conference on diabetic foot wound care: 7-8 april 1999, Boston, Massachusetts. American diabetes association. *Diabetes Care* 1999;22(8):1354-60.
- [8] Lazarus GS, Cooper DM, Knighton DR, et al. Definitions and guidelines for assessment of wounds and evaluation of healing. *Arch Dermatol* 1994;130(4):489-93.
- [9] Fang XP, Xia WS, Sheng QH, et al. Purification and characterization of an immunomodulatory peptide from bovine placenta water-soluble extract. *Prep Biochem Biotechnol* 2007;37(3):173-84.
- [10] O'Keefe EJ, Payne RE, Russell N. Keratinocyte growth promoting activity from human placenta. *Journal of cellular Physiology* 1985;124(3):439-45.
- [11] Carotti D, Allegra E. An approach to chemical characterization of human placental extracts: proteins, peptides, and amino acids analyses. *Physiol Chem Phys* 1981;13(2):129-36.
- [12] Ramachandran A, Das AK, Joshi SR, et al. Current status of diabetes in India and need for novel therapeutic agents. *Supplement to japi* 2010;58:7-9.
- [13] Falanga V. Wound bed preparation: science applied to practice. *European wound management association. Position document: Wound bed preparation in practice* 2004:2-5.
- [14] Centers for Disease Control and Prevention. *Data and Trends: National Diabetes Surveillance System, Vol. 2006, National Center for Chronic Disease Prevention and Health Promotion, Atlanta, 2005.*
- [15] Aziz Z, Lin WK, Nather A, et al. Predictive factors for lower extremity amputations in diabetic foot infections. *Diabetic foot & ankle* 2011;2:7463-7.
- [16] Young MJ, Boulton AJ, Williams DR, et al. A multicentre study of the prevalence of diabetic neuropathy in the United Kingdom hospital clinic population. *Diabetologia* 1993;36(2):150-4.
- [17] Lipsky BA, Armstrong DG, Citron DM, et al. Ertapenem versus piperacillin/tazobactam for diabetic foot infections (SIDESTEP): prospective, randomized, controlled, double-blinded, multicentre trial. *Lancet* 2005;366(9498):1695-703.
- [18] Hartemann-Heurtier A, Robert J, Jacqueminet S, et al. Diabetic foot ulcer and multidrug-resistant organisms: risk factors and impact. *Diabet Med* 2004;21(7):710-5.
- [19] Lipsky BA, Berendt AR, Deery HG, et al. Diagnosis and treatment of diabetic foot infections. *Clin Infect Dis* 2004;39(7):885-910.
- [20] Chakraborty PD, Bhattacharyya D. Isolation of fibronectin type III like peptide from human placental extract used as wound healer. *Journal of Chromatography B* 2005;818(1):67-73.
- [21] Datta P, Bhattacharyya D. In vitro growth inhibition of microbes by human placental extract. *Curr Sc* 2005;88:782-6.
- [22] Navadiya SK, Patel MP, Vaghani YL. Study of topical placental extract versus povidone iodine and saline dressing in various diabetic wounds. *Natl J Med Res* 2012;2(4):411-3.
- [23] Frykberg RG, Lavery LA, Pham H, et al. Role of neuropathy and high foot pressures in diabetic foot ulceration. *Diabetes Care* 1998;21(10):1714-9.