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Original Article

The high lymphadenopathy and subcutaneous edema are associated with development of foot ulcer in type 2 diabetes: A collagen implanted antibiotic therapy

Karthikeyan Elumalai[a,b,*], Chittiboyena Sai Chaithanya Yadhav[a], Shaik Sana Nishad[a], Sivaneswari Srinivasan[c], Kamani Mounika[a], Srinivasan Sivannan[d], Kota Supriya[a], Anil Kumar[a]

[a] Department of Postgraduate Research in Clinical Pharmacy, Santhiram College of Pharmacy, Nandyal 518 501, India
[b] Department of Medicinal Chemistry, The Oxford College of Pharmacy, Hongasandra, Bangalore 560 068, India
[c] Department of Pharmaceutics, K.K. College of Pharmacy, Gerugambakkam, Chennai 600 128, India
[d] Department of Pharmacy Practice, TVM College of Pharmacy, Ballari 583 103, India

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ABSTRACT

The infective diabetic foot ulcer was caused by the high microbial infection affecting the surrounding tissue of the foot. The distal region of a foot was affected by the microbial infection in an uncontrolled situation. In this study, the possible efforts were made to prevent the diabetic foot ulcer of a patient. The diabetic foot ulcer, with tissue exposure and microbial infection on the surface of the foot, was treated with several antibiotics and dressings. The revascularization treatment procedure was started. The infection was reduced when compared with the beginning of this treatment. The collagen implant along with Gentamicin sulphate found that collagen was penetrated into the wound and helped the granulation of the tissue formation. The topical gentamicin reduced the bacterial contamination and cicatrization. The infective diabetic foot ulcer was treated by weekly dressings with collagen implant Gentamicin sulphate, Doxycycline, and Vancomycin therapy. It suggests that this combination will accelerate the healing of diabetic foot ulcer.

1. Introduction

The physically damaged surface area of the skin and underlying tissues are the major cause of the skin ulcer. However, in a diabetic condition, most skin ulcers occur on the legs and feet. Ulcer healing process is delayed and takes more time in the diabetic foot ulcer [1,2]. The novel therapeutic agents are needed for the treatment of diabetic associated foot ulcers. Although numerous studies aiming to investigate the mechanisms and the path of wound healing of skin ulcer performed in the rodent dorsal region, the healing procedure differs in the human feet [3,4].

The rodent dermis is bounded by panniculus carnosaurs which accelerate wound contraction immediately after incisions [5]. In humans, wound healing process occurs after the formation of a collagen-rich matrix which is produced by migrated fibroblasts [6]. In other words, the dominant processes in the early stage of wound healing are re-epithelialization and granulation in humans, whereas contraction in rodents [7]. The presence of diabetic foot ulcer may have a major impact on the health-related quality of life (HRQL) in patients found with the current ulcer. The existence of other diabetic complications and the conduct of a major amputation were the most negative variables explaining patients' HRQL scores [8–11]. Using the comprehensive clinical assessments [12] it is found that, the higher ages of the association had Type 2 diabetes which increased the severity of foot ulcers and the presence of more than one ulcer were all significant and independent predictors of HRQL. We herein report that rare diabetic foot ulcer in a patient who received vigorous fluid resuscitation was successfully recovered and discharged after a month.

2. Case report

A 60-year-old male patient with non-insulin treated Type 2 diabetes which was reported to the emergency department on eighteenth November 2015 because of a third-degree wound with 12 × 10 cm on the right instep with an exposed tendon Fig. 1A. Additionally, he had a fever and inflammatory signs around the wound and left arterial abnormality associated with sinus tachycardia, lymphadenopathy, and subcutaneous edema, even the distal pulses were noted on physical

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* Corresponding author.
E-mail address: karthikeyanelumalai@hotmail.com (K. Elumalai).

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Fig. 1. Relationship between initial and Eight Weeks Foot Ulcer Therapy A: Wound beginning of the Treatment. B: Clinical result after eight weeks.

examination. The patient did not refer claudication and blood flow was noted on Doppler. The empirical antibiotic therapy with Meropenem and Gentamicin sulphate tablet the treatment was started without knowing the microbial infection. The patient was admitted to the general surgery department for wound care. The exudates were sent to microbial culture, and it was positive for Enterococcus species.

The granulated tissue was slowly growing in the wounded area, no significant improvement was achieved with the treatment. The wound was almost the same size with exposed tendon because of that a skin graft was tried in a dressing and antibiotic therapy for a week. Later it was diagnosed as ischemic foot ulcer. Only 15% of the grafts were viable on the tenth postoperative day. Ten days later infection recurred with a positive culture for Enterococcus species, the microorganism was sensitive to Gentamicin, Meropenem, Vancomycin, and Doxycycline. The treatment decision was made from collagen implant impregnated Gentamicin sulphate dressings (topical therapy Size of the patch was 2:5.8 cm) on daily basis and he was discharged after a month. The outpatient consultation during follow-up included collagen implant impregnated with gentamicin sulphate (Collatamp) dressings, on a weekly basis. A good progress was noted with granulation tissue growing on the wound area and epithelization coming from the wound edges. At the eighth week of outpatient dressings, cicatrization was 75% complete Fig. 1B. After three months of Collatamp dressings, the wound was completely epithelized. The patient was very happy with the improvement as no infection, no pain occurred during Collatamp treatment and no recurrence during the therapy.

3. Discussion

The diabetic foot ulcer is defined as ulceration of tissues, due to the peripheral neurological abnormalities, mainly by the bacterial infection [2]. The ulceration mechanism depends upon the pathophysiological, anatomical changes and environmental influence [6]. The pathophysiological changes lead the peripheral vascular disease. The environmental factor influences the infection and it acts as a precursor for ulceration. The peripheral arterial disease (PAD) is common in diabetic patients, the PAD increases the risk of atherosclerosis formation [1]. The statistical data of the literature survey, suggests that 3–4% of diabetic patients suffer from foot ulcer in their lifetime [9].

In this case, the epithelization of the wound was not possible for first one week therapy because bacterial infection decreases the cicatrization and granulation of tissue (the infection is caused by Enterococcus species). The increased blood pressure may cause the foot ulcer, due to the decreased elasticity of the arteries in Type 2 diabetes [19]. The vascular diseases may be caused by internal hyperglycemia and other metabolic disorder. The increased blood sugar maintenance is a primary criterion for the treatment of foot ulcer. The normal blood sugar level is maintained by oral hypoglycemic agents and the vascular disease is treated by vasodilators. The collagen implant with Gentamycin sulphate is used to reduce the surgical infection in cardiac, general and orthopedic surgery. The Gentamicin is a broad spectrum bactericidal antibiotic, that produces the antibacterial action by irreversibly binding to the 30S subunit of the bacterial ribosome, interrupting protein synthesis [13–15]. The topical application of collagen implant of Gentamycin enhances the minimum inhibitory concentration (MIC) and shows low levels of toxicity because it has no systemic absorption. The microorganisms do not exhibit any resistance towards Gentamycin [16–19]. The collagen implant with Gentamycin, when applied to the wounded surface, increased the tissue granulation. The collagen act as the carrier has effects on treatment, helpful to the hemostasis, reduces scarring, has poor antigenicity, and it is a well-tolerated implant without side effects [20]. The healing process gets faster once treated with Collatamp with Gentamycin sulphate, Meropenem, Doxycycline, and Vancomycin.

The lymphadenopathy, subcutaneous edema and PAD are major modifiable risk factors of previous studies [11,17,19]. The result obtained from this study, matches with other study data. The randomized controlled study trial published by Lipsky et al. on diabetic foot ulcer treatment comparison says that the test group with collagen implant Gentamycin sulphate sponge produces higher healing rate when compared with the control group [20]. The Varga et al. reported that the collagen implant gentamycin sulphate decreased wound healing in diabetics by almost fourteen days [19,21]. Our study result similar costa report, in that study collagen implanted Gentamicin sulphate and prostaglandins used for the treatment of foot ulcer, it took five months to completely cure the foot ulcer [1]. In our study, we used gentamicin-collagen, doxycycline, and vancomycin combination for the treatment of diabetic foot ulcer, this combination completely cured the disease with in three-month therapy. In the six month follow up of this study no lymphadenopathy, subcutaneous edema and PAD was not observed in our study.

In a case where diabetic patient with chronic ischemia of lower limbs, without the chance of epithelization which leads to an ulcer, can be treated with antibiotic combination therapy where the granulation tissue formation and epithelization can be achieved. The ischemia raises the amputation rate of a diabetic patient, so all the efforts were made to decrease the chance of amputation; hence Collatamp is the preferable choice for treatment of diabetic foot ulcer.

4. Conclusions

In this exploratory clinical study proves the potential efficacy and safety of gentamicin-collagen, doxycycline, and vancomycin for the treatment of diabetic foot ulcer. This combination completely removed necrotic tissue without damaging healthy normal tissue. The result shows that wound surface area has reduced due to the granulation of tissues. The result suggests that gentamicin-collagen and antibiotics combination will accelerate the healing of foot ulcers. The results need to be further confirmed in a large randomized controlled clinical trial, which is ongoing in our tertiary care teaching hospital.

Conflicts of interest

All authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bfopcu.2018.03.002.

References

[1] C.E. Costa Almeida, Collagen implant with gentamicin sulphate as an option to treat a neuroischaemic diabetic foot ulcer: case report, Int. J. Surg. Case Rep. 21 (2016) 48–51.
[2] R.G. Frykberg, Epidemiology of the diabetic foot: ulcerations and amputations, Adv. Wound Care 12 (1999) 139–141.
[3] Xu. Junwang, Wu. Wenjie, L. Zhang, W.D. Martin, M.W. Morris, M.E. Mitchell, K.W. Liechty, The role of micro RNA-146a in the pathogenesis of the diabetic wound-healing impairment: correction with mesenchymal stem cell treatment, Diabetes 61 (2012) 2906–2912.
[4] X. Yan, B. Chen, Y. Lin, Y. Li, Z. Xiao, X. Hou, Q. Tan, J. Dai, Acceleration of diabetic wound healing by collagen-binding vascular endothelial growth factor in diabetic rat model, Diabetes Res. Clin. Pract. 90 (2010) 66–72.
[5] A. Tallis, T.A. Motley, R.P. Wunderlich, J.E. Dickerson, C. Waycaster, H.B. Slade, Clinical and economic assessment of diabetic foot ulcer debridement with collagenase: results of a randomized controlled study, Clin. Thera. 35 (2013) 1805–1820.
[6] K.J. Sonnemann, W.M. Bement, Wound repair: toward understanding and integration of single-cell and multicellular wound responses, Annu. Rev. Cell Dev. Biol. 27 (2011) 237–263.
[7] W.J. Jeffcoate, The incidence of amputation in diabetes, Acta Chir. Belg. 105 (2005) 140–144.
[8] W.J. Jeffcoate, K.G. Harding, Diabetic foot ulcers, Lancet 361 (2003) 1545–1551.
[9] L. Abetz, M. Sutton, L. Brady, P. McNulty, D. Gagnon, The Diabetic Foot Ulcer Scale (DFS): a quality of life instrument for use in clinical trials, Pract. Diabetes Intern 19 (2002) 167–175.
[10] J.W. Meijer, J. Trip, S.M. Jaegers, Quality of life in patients with diabetic foot ulcers, Disability Rehabil. 23 (2001) 336–340.
[11] F.M.H. Nabuurs, M.S. Huijberts, K.A.C. Nieuwenhuijzen, J. Willems, N.C. Schaper, Health related quality of life of diabetic foot ulcer patients and their caregivers, Diabetology 48 (2005) 1906–1910.
[12] P. Valensi, I. Girod, F. Baron, D.T. Moreau, P. Guillon, Quality of life and clinical correlates in patients with diabetic foot ulcers, Diabetes Metab. 31 (2005) 263–271.
[13] G.E. Reiber, L. Vileikyte, E.J. Boyko, D.J. Smith, L.A. Lavery, A.J.M. Boulton, Causal pathways for incident lower extremity ulcers in patients with diabetic from two settings, Diabetes Care 22 (1999) 157–162.
[14] J.A. Mayfield, G.E. Reiber, L.J. Sanders, D.J. Janisse, L.M. Pogach, Preventive foot care in people with diabetes, Diabetes Care 21 (1998) 2161–2177.
[15] G.D. Valk, D.M. Kriegsmann, W.J.J. Assendelft, Patient education for preventing diabetic foot ulceration: a systematic review, Endcrinol. Metab. Clin. Nat. Am. 31 (2002) 633–658.
[16] M. Peppa, P. Stavroulakis, S.A. Raptis, Advanced glycoxidation products and impaired diabetic wound healing, Wound Repair Regen. 17 (2009) 446–472.
[17] J. Apelqvist, K. Bakker, H.W.H. Van, N.C. Schaper, Practical guidelines on the management and prevention of the diabetic foot: based upon the International Consensus on the Diabetic Foot prepared by the International Working Group on the diabetic foot, Diabetes Metab. Res. Rev. 24 (2008) (2007) 181–187.
[18] S. Xutian, J. Zhang, W. Louise, New exploration and understanding of traditional Chinese medicine, Am. J. Chin. Med. 37 (2009) 411–426.
[19] B. Mendel, A.D. Wendy, M.E.D. Timothy, A longitudinal study of foot ulceration and its risk factors in community-based patients with type 2 diabetes: the Fremantle Diabetes study, Diabetes Res. Clin. Pract. 106 (2014) 42–49.
[20] B.A. Lipsky, M. Kuss, M. Edmonds, A. Reyzelman, F. Sigal, Topical application of a gentamicin -collagen sponge combined with systemic antibiotic therapy for the treatment of diabetic foot infections of moderate severity: a randomized, controlled, multicentre clinical trial, J. Am. Pod. Med. Assoc. 102 (2012) 223–232.
[21] M. Varga, B. Sixta, R. Bem, I. Matia, A. Jirkovska, M. Adamec, Application of gentamicin -collagen sponge shortened wound healing time after minor amputations in diabetic patients-a prospective: randomised trial, Arch. Med. Sci. 10 (2014) 283–287.