CASE REPORT

Limb Saving with a Combination of Allogenic Platelets-Rich Plasma, Fibrin Glue, and Collagen Matrix in an Open Fracture of the Tibia: A Case Report

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Abstract

Tibia open fractures and lower limb soft tissue injuries are undesired conditions for orthopedic and general surgeons, and there is no ideal procedure for treating recalcitrant ulcers or severe traumatic ulcers. Recently, several novel approaches have been proposed, such as bone marrow stem cells, platelets, fibrin glue, and collagen matrix. The current study was conducted to evaluate the effectiveness of combining platelets, fibrin glue, and a collagen matrix for treating a serious limb-threatening wound in a 33-year-old male with a right lower limb injury. After treatment, the wound was fully closed, tissue granulation was grown, skin grafting was done, and the right leg was saved. In conclusion, the combination of the mentioned components can be utilized to synergistically enhance wound healing and preserve the limb.

Level of evidence: V

Keywords: Collagen matrix, Fibrin glue, Limb-threatening wound, Platelets-rich plasma

Introduction

Serious open fractures of the tibia are devastating and, in numerous cases, they ultimately lead to amputation.[1] Non-healing wounds are correlated with a high percentage of morbidity and mortality and have an adverse effect on the lives of patients.[2,3] The cost imposed on the health system for non-healing wounds has been calculated to be approximately $70,000.[4] The tibia fractures are the most common type of lower extremity fractures[5,6] and are considered a challenge to orthopedic and plastic surgeons.[6] High-grade open tibial fractures usually need complicated reconstruction with advanced soft tissue coverage methods to improve fracture and wound healing.[7] The British Orthopaedic Association Standards for Trauma instructions suggest that open fractures of the lower extremity should be managed in a tertiary referral center, irrespective of any specific time frame.[8]

The management procedures for the limb injury as suggested by Xu YQ et al., include antibiotic administration, serial debridement, bone grafting if needed, and the application of various flaps (free thoraco-umbilical, gastrocnemius muscular flaps, sural neurocutaneous vascular, saphenous neurocutaneous vascular, and fasciocutaneous), and various external fixators (Hybrid fixators, half-ring, AO, unilateral axial dynamic, and Weifang).[9]

Open tibial fractures typically occur with high-velocity harm, and such cases can cause serious harm to other limbs and body parts.[10] Court-Brown et al. reported that 21% of patients with an open long bone fracture had an Injury Severity Score of more than 15 and that 45% experienced other substantial musculoskeletal injuries .[5]

Offloading, debridement, and supplementary treatments are current therapies for non-healing wounds. However, the response to these treatments often yields poor outcomes and proves to be disappointing.

In platelets, there are biologically active granules known as α-granules and dense granules Alpha-granule has some cytokine and bioactive factors, such as insulin-like growth factor (IGF-I, IGF-II), fibroblast growth factor, transforming growth factor-β, platelet-derived growth factor, vascular endothelial growth factor, and epidermal growth factor.

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These factors and cytokine have a significant impact on the steps of wound healing, including cell proliferation, cell differentiation, and neovascularization. [11,12]

Here, we present a combined application of platelet growth factors, collagen matrix, and fibrin glue as a delivery vehicle for the sustainable release of platelet-fibrinogen rich plasma (PFRP)-derived bioactive factors. This approach aims to promote healing in refractory ulcers.

Case Presentation

A 33-year-old farmer, who sustained a serious limb-threatening wound and an open fracture of the tibia due to a collision with a Gleaner combine, was referred to the Shahid Kamyab Trauma Referral Center (Academic Hospital of Mashhad University of Medical Sciences), Mashhad, Iran. A Gustilo IIIB open tibia fracture was diagnosed during the first consultation with the general surgeon and orthopedic surgeon. The patient had no past medical history of chronic diseases, infections, or other diseases. Upon arrival at the care center, he exhibited good hemodynamic status. The medical consultation committee recommended amputating the right leg from the knee, but the patient disagreed and asked for alternative solutions. So external fixation, a treatment combining the use of a collagen matrix, allogeneic platelet-rich plasma, and fibrin glue, along with autologous skin grafting were suggested for the patient. The patient demonstrated understanding, was able to read, and expressed satisfaction with signing the informed consent form.

The fibrin glue and platelets were prepared using standard methods. A total of 350 cc of peripheral blood was collected from a blood group match donor into 400 cc triple blood donation bags. The platelets were separated through two rounds of centrifugation: the first at 1,800 × g for 5 minutes, followed by the second at 3,500 × g for 10 minutes. The supernatant plasma was then isolated, resulting in the obtainment of 25 cc of platelet-rich plasma.[13] The fibrinogen concentrate can be obtained from the plasma using two different biochemical procedures (i.e., the cryoprecipitate procedure or the ethanol precipitation procedure).[14] In the coprecipitation procedure, the plasma was subjected to a -75°C freeze followed by a 3°C thaw. Then, the plasma was centrifuged at 6,500 × g for 5 minutes. The supernatant plasma was removed to a final volume of 25cc. In the ethanol precipitation procedure, absolute ethanol at 0°C was added to 10% v/v plasma. Fibrinogen was collected by centrifugation at 6,000 × g for 20 minutes, and the supernatant plasma was eliminated to the final volume of 25 cc. Finally, a total of 25cc of concentrated fibrinogen mixed with platelets (final volume 50cc: PFRP) was obtained. One milliliter of thrombin was created by adding 10% calcium gluconate to the removed plasma. Viral inactivation of PFRP and thrombin was done by incubating them at 62°C for one hour. Afterward, it is stored in a -20°C freezer until use, with a maximum storage period of three months. Before the application of PFRP, the devitalized and necrotic area of the wound was surgically debrided until macroscopic bleeding was observed. This resulted in the PFRP coming into contact with living tissue of the wound. When using PFRP, a 50-cc volume of PFRP was mixed with calcium gluconate and 1 ml of thrombin. Subsequently, the collagen matrix (Surgicoll ®; MBP, Medical Biomaterial Products, GmbH, Tehran, Germany) was immediately impregnated with 51cc of the resulting mixture and placed on the wound.

Finally, a paraffin gauze was placed over the wound and secured with a rolled gauze bandage. After two days, the whole dressing was removed and the wound was irrigated with a solution of isotonic sodium chloride. The whole process mentioned above was repeated every two days for granulation tissue formation and wound closure. The patient was regularly observed for ulcer closure, the orthopedic condition of bone fracture, and any other possible complications. After a complete tissue granulation in the wound, plastic surgeons and orthopedic surgeons performed multiple surgeries for skin grafting. Figure 1 displays the sequential photographs of the patient. [Figure 1] After four months of orthopedic treatment, multiple surgeries, and grafting, a viable and functional leg was successfully achieved.

Figure 1. Serial photography of the treatment of the patient. (A) Leg wound before the surgery, (B) Surgical intervention and necrotic tissue removal, (C) Tissue granulation following the application of allogeneic platelet-rich plasma, fibrin glue, and collagen matrix, (D) Skin grafting after tissue granulation, (E) Fully healed limb

Discussion

This study reports a patient with a recalcitrant and limb-threatening wound that was treated using a combination of fibrin glue, allogeneic platelets, and collagen matrix. Guidelines from the British Orthopaedic Association recommend amputation when the projected functional outcome following reconstruction is expected to be worse than that of a trans-tibial amputation.[8] Reuss et al. demonstrated that while time (up to 48 hours) was not a main factor in predicting infection and nonunion, increased severity of the fracture and the frequency of debridement were important factors in predicting infection rate and the development of infection, respectively. In addition, they stated that the infection rate for fractures initially treated with external fixation and subsequently with intramedullary (IM) nailing was significantly higher compared to fractures treated solely with IM nailing.[15]

Traditionally, debridement, external fixation, and delayed soft-tissue closure had been used to manage open tibial fractures.[16-18] Today, due to the proven role of autologous and allogeneic platelet-rich plasma (PRP) in stimulating tissue growth and regeneration, it can be used alongside traditional methods to accelerate repair in non-healing wounds.[19, 20]

Franchini et al. employed the platelet gel (autologous platelet concentrate and cryoprecipitate) in different operations, primarily oral and maxillofacial surgery, for 19 patients. Physiologic bone structure reconstruction and the improved osteoblastic reaction were observed in all patients, with no negative reactions.[21]

Some authors who are war surgeons have reported the functional results of transtibial amputees from the Vietnam War.[22]

Crovetti et al. investigated the efficiency of the weekly application of allogenic for 21 patients and autologous for 3 patients platelet gel (PG) in healing cutaneous refractory wounds with different etiologies. In their study, 9 patients achieved complete healed, 9 patients showed partial response, 2 patients received cutaneous grafts, and 4 patients discontinued treatment. While pain reduction was reported with the application of PG, it is worth noting that neither clinicians nor patients were blinded to the treatment, potentially introducing bias to the self-reporting of pain.[23]

Mandible defects were treated with PRP administration on the affected side.[24] the findings of a study by Kanthan et al. demonstrated the favorable use of PRP in non-uniting segmental tibial defects in an animal model.[25]

The results of this study have demonstrated the feasibility of our method as a non-invasive approach in the treatment of limb-threatening wounds. The application of PFRP-collagen therapy, which involves a combination of continuous and immediate release of growth factors, significantly healed or reduced the size of recalcitrant ulcers. There was no evidence of systemic or local complications associated with the method. Based on our findings, we have been prompted to conduct a larger study to further assess the effectiveness of PFRP-collagen therapy in treating recalcitrant ulcers, wounds, and injuries. Additionally, considering the authors' experience in stem cell therapy,[26] the authors suggest that for patients who do not respond to the PFRP-collagen therapy, by considering the pathological factors related to the phenotypically changed and/or senescent mesenchymal cells in the ulcer, stem cell therapy could be pursued as an alternative method for curing recalcitrant ulcers.

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References

1. Fairhurst M. The function of below knee amputees versus the patient with salvaged grade-III tibial fracture. Clin Orthop. 1994 ;(301):227-32.
2. Brod M. Quality of life issues in patients with diabetes and lower extremity ulcers: patients and care givers. Qual Life Res. 1998; 7(4):365-72. doi: 10.1023/a:1024994232353.
3. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA. 2005; 293(2):217-28. doi: 10.1001/jama.293.2.217.
4. Garber SL, Rintala DH. Pressure ulcers in veterans with spinal cord injury: a retrospective study. J Rehabil Res Dev. 2003; 40(5):433-41. doi: 10.1682/jrrd.2003.09.0433.
5. Court-Brown CM, Rimmer S, Prakash U, McQueen MM. The epidemiology of open long bone fractures. Injury. 1998; 29(7):529-34. doi: 10.1016/s0020-1383(98)00125-9.
6. Chua W, Murphy DP, Siow W, Kagda FH, Thambiah J. Epidemiological analysis of outcomes in 323 open tibial diaphyseal fractures: a nine-year experience. Singapore Med J. 2012; 53(6):385-9.
7. Pollak AN, McCarthy ML, Burgess AR. Short-term wound complications after application of flaps for coverage of traumatic soft-tissue defects about the tibia. The Lower Extremity Assessment Project (LEAP) Study Group. J Bone Joint Surg Am. 2000;82(12):1681-91.

8. BOAST. Guideline to lower limb open fractures. Available at: www.bapras.org.uk/downloaddoc.asp?id=141. Accessed July 31, 2012.
9. Xu YQ, Lin YQ, Li J, et al. Repair and reconstruction of severe leg injuries: retrospective review of eighty-five patients. Chin J Traumatol. 2006; 9(3):131-7.
10. Jagdev SS, Pathak S, Kanani H, Salunke A. Functional Outcome and Incidence of Osteoarthritis in Operated Tibial Plateau Fractures. Arch Bone Jt Surg. 2018 Nov;6(6):508-516. PMID: 30637306; PMCID: PMC6310186.
11. Aslani, H., Nourbakhsh, S. T., Zafarani, Z., Ahmadi-Bani, M., Ananloo, M. E. S., Beigy, M., & Salehi, S. (2016). Platelet-rich plasma for frozen shoulder: a case report. Archives of Bone and Joint Surgery, 4(1), 90.
12.Shafieian R, Matin MM, Rahpeyma A, Fazel A, Sedigh HS, Nabavi AS, Hassanzadeh H, Ebrahimzadeh-Bideskan A. Effects of Human Adipose-derived Stem Cells and Platelet-Rich Plasma on Healing Response of Canine Alveolar Surgical Bone Defects. Arch Bone Jt Surg. 2017 Nov;5(6):406-418. PMID: 29299496; PMCID: PMC5736890.
13. Whitman DH, Berry RL, Green DM. Platelet gel: an autologous alternative to fibrin glue with applications in oral and maxillofacial surgery. J Oral Maxillofac Surg. 1997; 55(11):1294-1299. doi: 10.1016/s0278-2391(97)90187-7.
14. Silver FH, Wang MC, Pins GD. Preparation and use of fibrin glue in surgery. Biomaterials. 1995; 16(12):891-903. doi: 10.1016/0142-9612(95)93113-r.
15. Reuss BL, Cole JD. Effect of delayed treatment on open tibial shaft fractures. Am J Orthop (Belle Mead NJ). 2007; 36(4):215-20.
16. Gopal S, Giannoudis PV, Murray A, Matthews SJ, Smith RM. The functional outcome of severe, open tibial fractures managed with early fixation and flap coverage. J Bone Joint Surg Br. 2004; 86(6):861-7. doi: 10.1302/0301-620x.86b6.13400.
17. Gustilo RB. Current concepts in the management of open fractures. Instr Course Lect. 1987; 36:359-66.
18. Blick SS, Brumback RJ, Lakatos R, Poka A, Burgess AR. Early prophylactic bone grafting of high-energy tibial fractures. Clin Orthop Relat Res. 1989 ;(240):21-41.
19. Alsousou J, Thompson M, Hulley P, Noble A, Willett K. The biology of platelet-rich plasma and its application in trauma and orthopaedic surgery: a review of the literature. J Bone Joint Surg Br. 2009; 91(8):987-96. doi: 10.1302/0301-620X.91B8.22546.
20. Anitua E, Sánchez M, Orive G, Andia I. Delivering growth factors for therapeutics. Trends Pharmacol Sci. 2008; 29(1):37-41. doi: 10.1016/j.tips.2007.10.010.
21. Franchini M, Dupplicato P, Ferro I, De Gironcoli M, Aldegheri R. Efficacy of platelet gel in reconstructive bone surgery. Orthopedics. 2005; 28(2):161-3. doi: 10.3928/0147-7447-20050201-19.
22. Dougherty P. Transtibial amputees from the Vietnam War: twenty-eight year follow-up. J Bone Joint Surg Am. 2001; 83(3):383-9. doi: 10.2106/00004623-200103000-00010.
23. Crovetti G, Martinelli G, Issi M, et al. Platelet gel for healing cutaneous chronic wounds. Transfus Apher Sci. 2004; 30(2):145-151. doi: 10.1016/j.transci.2004.01.004.
24. Malhotra A, Pelletier MH, Yu Y, Walsh WR. Can platelet-rich plasma (PRP) improve bone healing? A comparison between the theory and experimental outcomes. Arch Orthop Trauma Surg. 2013; 133(2):153-65. doi: 10.1007/s00402-012-1641-1.
25. Kanthan SR, Kavitha G, Addi S, Choon DS, Kamarul T. Platelet-rich plasma (PRP) enhances bone healing in non-united critical-sized defects: a preliminary study involving rabbit models. Injury. 2011; 42(8):782-9. 10.1016/j.injury.2011.01.015.
26. Ravari H, Hamidi-Almadari D, Salimifar M, Bonakdaran S, Parizadeh MR, Koliakos G. Treatment of non-healing wounds with autologous bone marrow cells, platelets, fibrin glue and collagen matrix. Cytotherapy. 2011; 13(6):705-11. doi: 10.3109/14653249.2011.553594.