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CASE REPORT

Delayed union of the clavicle treated with plasma rich in growth factors

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Nonunion is an uncommon complication of fracture of the clavicle ; it is usually treated surgically. The use of biological treatments in this type of condition is increasingly more common because of their ease of application. Plasma rich in growth factors (PRGF) has been used in delayed healing and in nonunion of fractures. We report a case of delayed union fracture of the clavicle in which biological treatment was chosen before considering surgery. Three percutaneous injections of PRGF, one every 2 weeks, were delivered into the delayed union site. The autologous PGRF used was obtained through the patented PRGF® system. Three months after the final dose, computed tomography study showed healing of the bone. The patient regained complete mobility of the shoulder without pain. Currently she is able to carry out all the normal life activities and experiences no pain.

Key words : platelet-rich plasma ; nonunion ; clavicle fracture.

INTRODUCTION

The clavicle is the most commonly fractured bone in the body, accounting for 5% to 10% of all fractures (*5,19*). The reported incidence of nonunion is only 0.1% to 0.8% (*17,19*). When nonunion occurs, however, it can pose a difficult problem, causing pain and functional impairment of shoulder function (*12,23*). The resulting deformity or callus may cause compression of the brachial plexus or subclavian artery (*23,32*). Management of patients with symptomatic nonunion of the clavicle usually consists of surgery using various techniques, among which the most common is intramedullary fixation or rigid internal fixation with plates (*7*).

Fracture nonunion occurs when the normal biological healing processes of the bone cease, such that solid healing will not occur without further treatment. In these situations, careful assessment of the mechanical and biological factors contributing to the cause of nonunion can be used to direct treatment (*8,11,15,20*). Several crucial elements should be considered, for example, whether the nonunion is septic or aseptic (*25*) and whether it is hypertrophic, with an intact vascular supply, or atrophic, with little callus and an avascular and nonviable nonunion site. The latter is thought to be associated with a deficient biological process and may warrant the application of advanced biological technologies (*2,24*).

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The bioactivity of plasma rich in growth factors (PRGF) is based on a progressive and balanced release of a pool of proteins and growth factors known to stimulate fracture healing such as platelet-derived growth factor (PDGF), transforming growth factor-b1 (TGF-b1), and insulin-like growth factor (*3,21,31*). In this report, we describe a patient with delayed union of a fracture of the clavicle, in whom PRGF was successfully used for treatment.

CASE REPORT

A 44-year-old woman with no medical history of interest sustained a fracture of the distal left clavicle (fig 1) after an accidental fall on the street. The initial treatment was conservative because the fracture was considered stable and the patient would not consider surgery. She used a sling to rest the arm for 10 days. After that time she had only mild pain and chose to no longer use the sling. During follow-up, she continued with mild symptoms (pain with pressure on the fracture and limited range of motion).

Eight months after the injury, the patient consulted us because of pain and functional limitations, consisting of restricted arm flexion in the last 20º to 30º of abduction. Radiographs showed atrophic delayed union of the clavicle fracture (fig 2).

We then proposed to treat the delayed union with PRGF injections before considering a more aggressive treatment, such as internal fixation. Three percutaneous injections of PRP, one every two weeks, were delivered into the delayed union site. The autologous PRGF used was obtained through the patented PRGF® system (Biotechnology Institute, Vitoria, Spain) (*1-3,24*).

Three months after the final dose, computed tomography (CT) study showed healing of the bone (figs 3, 4). The patient regained complete mobility of the shoulder without pain. Currently she is able to carry out all the normal life activities and experiences no pain.

DISCUSSION

Delayed union or nonunion occurs in 5% to 10% of all fractures (*5,14,19*), although the incidence of nonunion in fractures of the clavicle is much lower (0.1% to 0.8%) (*17,19*). The complex process of bone healing is regulated by local and systemic elements (*18*), and many factors can contribute to impede healing, thereby leading to nonunion. Extensive trauma, a large fracture gap, unstable fracture fixation, premature mobilization, infection, extensive osteonecrosis, comorbidities, inadequate blood supply, and older age have all been identified as factors that are unfavorable for bone healing (*1,6,10,22*).

Fig. 1. — Initial radiograph showing fracture of the distal right clavicle.

Fig. 2. — Atrophic nonunion at 8 months.

Fig. 3. — Computed tomography 3 months after the last PRP injection shows solid union.

Fig. 4. — 3D CT reconstruction clearly shows the healed clavicle at 3 months.

None of these factors were identified in the case reported herein ; hence we attribute the delayed union to an unknown lack of biological factors.

Platelet-rich plasma is a concentration of autologous human platelets in a small volume of plasma and, because it is a concentration of platelets, it is also a concentration of growth factors secreted by platelets in the healing processes (*30*). One histologic study reported a significant increase in bone density in maxillofacial and oral bone defects treated with platelet gel (*30*).

The advocates of platelet-rich plasma use cite benefits such as increased bone and wound healing and a decreased incidence of postoperative infection, pain, and blood loss. Numerous studies have focussed on the use of platelet-rich plasma for a diverse range of clinical applications, including periodontal and oral surgery (*6,30*), maxillofacial surgery (*30*), cosmetic and plastic surgery (*16*), spinal fusion, coronary bypass surgery, and treatment of chronic skin and soft tissue ulcers (*3*).

Several platelet growth factors are released during fracture repair, and these can trigger the activation of proliferation and chemotaxis of mesenchymal cells, osteoblasts, and chondrocytes (*6*). Weibrich *et al* described the effect of growth factors produced by platelets and their average concentrations in platelet-rich plasma. They observed no differences in the concentrations of these factors linked to age or sex, although there is a relationship with the patient's serum platelet count (*29*). Whitman described the application of autologous platelet gel in oral and maxillofacial surgery as an alternative to the use of fibrin glue (*30*).

Several studies comparing various methods for obtaining platelet-rich plasma (*13,28*) have shown that different serum concentrations of growth factors are obtained and for this reason, different therapeutic effects can be produced. It is generally accepted that growth factors have an essential role in the healing process and tissue formation. In fact, all stages of the repair process are controlled by a wide variety of cytokines and growth factors acting locally as regulators of the most basic cell functions, using endocrine, paracrine, autocrine and intracrine mechanisms.

Growth factors influence many of the processes common to both tissue repair and disease, including angiogenesis, chemotaxis and cell proliferation ; they also control the synthesis and degradation of extracellular matrix proteins. Their mode of action is to bind to the extracellular domain of a target growth factor receptor, which, in turn, activates the intracellular signal-transduction pathways. The elucidation of some of the functions of growth factors in tissue repair has led to the conclusion that their

controlled temporal expression is crucial following surgical interventions and in the treatment of musculoskeletal disorders, including bone fractures, cartilage defects and muscle and tendon lesions (*2*).

The plasma rich in platelets used in our patient was obtained with the PRGF system, a method that has been patented in Europe, the USA, and the rest of the world. This system requires 20 cm^3 of the patient's peripheral blood to obtain 8 to 10 cm^3 of plasma rich in platelets. The steps to obtain this material are described in several studies by Anitua and Sanchez (*1-3,24*).

In vivo animal and human studies have demonstrated the efficacy of growth factors for stimulating ossification (*26,27*). Several studies in surgery patients have shown their efficacy in achieving more rapid bone consolidation, particularly when associated with the use of osteoconductive material, such as autologous and allogenic bone (*9,18*). As in the case presented, other authors have used percutaneous PRGF administration without osteoinductive tools to encourage consolidation of fractures in the phase of delayed union and in nonunion, with an excellent outcome (*4,24*).

Management of patients who have symptomatic nonunion in the distal clavicle has involved the use of various surgical techniques, the most common being either K-wire transacromial fixation with cerclage or hook plate fixation with bone grafting (*7*). The easy preparation, biosafety and versatility of platelet-rich preparations and their reduced cost have encouraged their therapeutic use for the stimulation of tissue healing and bone regeneration. Plasma rich in growth factors is a standardized and well-characterized platelet-rich preparation that has shown its versatility and efficacy in several medical areas (*2,3,15,24*).

On the other hand, in our case, other factors may have come into action, such as systemic drugs, quitting smoking habits, change in life, etc but we could not identify any factor that could account for a complete consolidation of the delayed fracture. The effect of repetitive needling of the fracture site may also have had some action in healing of the delayed union. We need more studies with placebo or control group to determinate the value of platelet-rich plasma in fracture healing.

REFERENCES

1. **Anitua E, Andia I, Ardanza B, Nurden P, Nurden AT**. Autologous platelets as a source of proteins for healing and tissue regeneration. *Thromb Haemost* 2004 ; 91 : 4-15.
2. **Anitua E, Sanchez M, Nurden AT *et al*.** New insights into and novel applications for platelet-rich fibrin therapies *Trends in Biotechnology* 2006 ; 24 : 227-234.
3. **Anitua E, Sanchez M, Orivea G, Andía I.** The potential impact of the preparation rich in growth factors (PRGF) in different medical fields. *Biomaterials* 2007 ; 28 : 4551-4560.
4. **Bielecki T, Gazdzik TS, Szczepanski T.** Benefit of percutaneous injection of autologous platelet-leukocyte-rich gel in patients with delayed union and nonunion. *Eur Surg Res* 2008 ; 40 : 289-296.
5. **Boehme D, Curtis RJ, Dehaan JT *et al.*** Non-union of the mid-shaft of the clavicle. *J BoneJoint Surg* 1991 ; 73-A : 1219-1226.
6. **Carlson ER**. Bone grafting the jaws in the 21st century : The use of platelet-rich plasma and bone morphogenetic protein. *Alpha Omegan* 2000 ; 93 : 26-30.
7. **Eskola A, Vaianionpaa S, Myllynen P**. Surgery for ununited clavicular fracture. *Acta Orthop Scand* 1986 ; 57 : 366-367.
8. **Evans RNO, Goldberg JA**. Reoperated clavicular nonunion treated with osteogenic protein 1 and electrical stimulation. *J Shoulder Elbow Surg* 2004 13 : 573-575.
9. **Gandhi A, Bibbo C, Pinzur M, Lin S**. The role of platelet-rich plasma in foot and ankle surgery. *Foot Ankle Clin* 2005 ; 10 : 621-637.
10. **Gandhi A, Doumas C, O'Connor JP, Parsons JR, Lin SS**. The effects of local platelet rich plasma delivery on diabetic fracture healing. *Bone* 2006 ; 38 : 540-546.
11. **Johnson EW Jr, Collins HR**. Nonunion of the clavicle. *Arch Surg* 1963 ; 87 : 963-966.
12. **Jupiter JB, Leffert RD**. Non-union of the clavicle. *J Bone JointSurg* 1987 ; 69 : 753-760.
13. **Kevy SV, Jacobson MS**. Comparison of methods for point of care preparation of autologous platelet gel. *J Extra Corp Technol* 2004 ; 36 : 28-35.
14. **Kloen P, Doty SB, Gordon E *et al***. Expression and activation of the BMP signaling components in human fracture nonunions. *J Bone Joint Surg* 2002 ; 84-A : 1909-1918.
15. **Lieberman JR, Daluiski A, Einhorn TA**. The role of growth factors in the repair of the bone. Biology and clinical applications. *J Bone Joint Surg* 2002 ; 84-A : 1032-1044.
16. **Man D, Plosker H, Winland-Brown JE**. The use of autologous platelet-rich plasma (platelet gel) and autologous platelet-poor plasma (fibrin glue) in cosmetic surgery. *Plast Reconstr Surg* 2001 *;* 107 : 238-239.
17. **Manske DJ, Szabo RM**. The operative treatment of mid-shaft clavicular non-unions. *J Bone Joint Surg* 1985 ; 67-A : 1367–1371.

18. Marx RE. Platelet-rich plasma (PRP) : What is PRP and what is not PRP? *Implant Dent* 2001 ; 10 : 225-228.
19. Neer CS II. Nonunion of the clavicle. *JAMA* 1960 *;* 172 : 1006-1011.
20. Phieffer LS, Goulet JA. Delayed unions of the tibia. *J Bone Joint Surg* 2006 ; 88-A : 206-216
21. Raschke M. Quantification, localization, and expression of IGF-I and TGF-b1 during growth factor-stimulated fracture healing. *Calcif Tissue Int* 2004 ; 74 : 388-397.
22. Resnick D, Goergen T, Niwayama G. *Diagnosis of Bone Joint Disorders*. WB Saunders, Philadelphia, 1988. vol 1, pp 54-76
23. Rowe CR. An atlas of anatomy and treatment of midclavicular fractures. *Clin Orthop Relat Res* 1968 ; 58 : 29-42.
24. Sanchez M, Anitua E, Cugat R *et al*. Nonunions treated with autologous preparation rich in growth factors. *J Orthop Trauma* 2009 ; 23 : 52-59
25. Struijs PA, Poolman RW, Bhandari M. Infected nonunion of the long bones. *J Orthop Trauma* 2007 ; 21 : 507-511.
26. Tayapongsak P, O'Brien DA, Monteiro CB, Arceo-Diaz LY. Autologous fibrin adhesive in mandibular reconstruction with particulate cancellous bone and marrow. *J Oral Maxillofac Surg* 1994 ; 52 : 161-165.
27. Torres J, Tresguerres I, Tamimi F *et al*. Influence of platelet-rich plasma on bone regeneration : a histomorphometric study in rabbit calvaria. *Int J Oral Maxillofac Implants* 2007 ; 22 : 563-568.
28. Weibrich G, Kleis WK. Curasan PRP kit vs PCCS PRP system : collection efficiency and platelets counts of two differents methods for the preparation of platelet rich plasma. *Clin Oral Implants* 2002 ; 13 : 437-443
29. Weibrich G, Kleis WKG, Hafner G, Hitzler WE. Growth factor levels in platelet-rich plasma and correlations with donor age, sex, and platelet count. *J Cranio Maxillofacial Surg* 2002 ; 30 : 97-102
30. 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* 1977 ; 55 : 1294–1299
31. Wildemann B, Schmidmaier G, Ordel S *et al*. Cell proliferation and differentiation during fracture healing are influenced by locally applied IGF-I and TGF-b1 : comparison of two proliferation markers, PCNA and BrdU. *J Biomed Mater Res B Appl Biomater* 2003 ; 65-B : 150–156.
32. Wilkins RM, Johnston RM. Ununited fractures of the clavicle. *J Bone Joint Surg* 1983 ; 65-A : 773–778.