REVISIÓN
ARCHIVOS DE MEDICINA DEL DEPORTE

Volumen XXV
Número 147
2012
Págs. 536-541

THE ROLE OF PLATELET-RICH PLASMA (PRP) IN THE TREATMENT OF SPORTS INJURIES OF THE KNEE

EL PAPEL DEL PLASMA RICO EN PLAQUETAS (PRP) EN LAS LESIONES DEPORTIVAS DE LA RODILLA

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INTRODUCTION

Some authors have stated that the therapeutic use of autologous platelet-rich plasma (PRP) could be a potential advance in the stimulation and acceleration of soft-tissue healing and bone regeneration[1,2]. Platelets have a rich store of factors and cytokines within their alpha granules and dense granules, which makes PRP an appealing therapeutic alternative. Some of the important factors found within the alpha granules of the platelet include platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF), among others[1]. The dense granules of the platelet contain neuromodulators and inflammatory modulators such as histamine and serotonine. Platelets are stimulated to release these growth factors and cytokines by exposure either to collagen or to thrombin and calcium. The purpose of this review article is to summarize the existing knowledge on the role of PRP in the treatment of sports injuries of the knee based on the studies published in PubMed until 1 July 2011, and to make a rigorous review of the methodology and results of the various animal and clinical studies published so far on the topic.

ACL INJURIES

A collagen-PRP scaffold was used by Murray et al to treat a central ACL defect in vivo in a canine model[3]. Their hypothesis was that a beneficial biologic repair response can be induced by placing a collagen-platelet rich plasma (collagen-PRP) material into a central ACL defect. They used a collagen-PRP scaffold to treat a central ACL defect in vivo. In a first experiment, the histologic response in treated and untreated defects was evaluated at 3 and 6 weeks. In a second experiment, biomechanical testing of the treated ligaments was performed at 6 weeks and compared with the results of biomechanical testing of untreated defects at the same time-point. The percentage filling of the defects in the treated ACLs was significantly higher at both the 3- and 6-week time-points when compared with the untreated contralateral control defects. Biomechanically, the treated ACL defects had a 40% increase in strength at 6 weeks, which was significantly higher than the 14% increase in strength previously reported for untreated defects. The main conclusion was that placement of a collagen-PRP bridging scaffold in a central ACL defect can stimulate healing of the ACL histologically and biomechanically. The ACL fails to heal after suture repair. One hypothesis

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Aceptado: 19.12.2011 / Revisión nº 237

for this failure is the premature loss of the fibrin clot, or provisional scaffolding, between the two ligament ends in the joint environment. To test this hypothesis, in a porcine model a substitute provisional scaffold of collagen-PRP hydrogel was used by Murray et al to fill the ACL wound site at the time of suture repair and the structural properties of the healing ACLs evaluated 4 weeks after surgery[4]. The supplementation of suture repair with a collagen-PRP hydrogel resulted in significant improvements in load at yield, maximum load, and linear stiffness at 4 weeks. Their main conclusion was that use of a stabilized provisional scaffold, such as a collagen-PRP hydrogel, to supplement primary repair of the ACL can result in improved biomechanical properties at an early time point. However, Murray et al stated that further studies were needed to determine the long-term effect of primary repair enhancement[4].

Murray *et al,* reported that use of a collagen-PRP scaffold in a canine model can ameliorate histologic differences noted between healing extra-articular ligamentous wounds and non-healing intra-articular ligamentous wounds[5]. Their study supported the hypothesis that premature scaffold failure may play a key role in the normally expected failure of the ACL to heal after injury. However, in a porcine model the use of PRP alone to supplement suture repair of the ACL was ineffective[6].

Silva and Sampaio performed a prospective study in four groups of patients undergoing ACL reconstruction with hamstring tendons: without PRP; with PRP in femoral tunnels at the end of surgery; with PRP in femoral tunnels at the end of surgery and intra-articular at 2- and 4 weeks after surgery; with PRP activated with thrombin in the femoral tunnels[7]. All patients underwent magnetic resonance imaging (MRI) of the knee 3 months after surgery to evaluate the signal intensity of the fibrous interzone (FIZ) in the femoral tunnels. The authors did not find any difference among the groups when comparing the signal intensity of the FIZ on MRI.

Nin *et al,* compared the clinical and inflammatory parameters with the addition of platelet-derived growth factor (PDGF) in primary ACL reconstruction with bone-patellar tendon-bone (BPTB) allograft in a clinical prospective, randomized, double-blind study[8]. The use of PDGF, on the graft and inside the tibial tunnel, in patients treated with bone-patellar tendon-bone allografts had no discernable clinical or biomechanical effect at 2 years' follow-up. Nin et al also stated that more clinical studies were needed to show the efficacy and use of these factors in daily practice in ACL reconstruction[8].

Sanchez *et al,* presented a review on the present and future use of PRP in the reconstruction of the ACL[9]. Although their findings were not conclusive, the use of autologous PRP seemed to be safe, reproducible, and effective in mimicking the natural processes of soft tissue and bone healing. In another study the same authors investigated whether the application of a particular PRP preparation rich in growth factors (PRGF) during ACL surgery gives a potential advantage for better tendon graft ligamentization[10]. The clinical study was observational and retrospective (low grade of evidence), using hyaluronan injections as a control. Sanchez et al concluded that the use of PRGF influenced the histologic characteristics of tendon grafts, resulting in more remodeling compared with untreated grafts[10]. However, they also stated that although these preliminary results need to be evaluated in a randomized clinical trial, they provide useful information about the safety of PRGF and open new perspectives on autologous treatments for joint diseases.

Vogrin *et al,* tried to improve knee stability after ACL reconstruction with a hamstring graft and use of platelet-derived growth factors[11]. Platelet-leukocyte gel was produced from platelet-leukocyte-rich plasma prepared from a unit of whole blood in an autologous platelet separator. The gel was applied locally, after hamstring graft placement. Fifty patients were included in a prospective study: 25 in the platelet gel group, 25 in a control group. They evaluated anteroposterior knee stability with the KT-2000 arthrometer before surgery and at 3 and 6 months after surgery. Patients treated with the gel demonstrated significantly better anteroposterior knee stability

than patients in the control group. The calculated improvements in knee stability at 6 months were 1.3 +/- 1.8 mm in the control group and 3.1 +/- 2.5 mm in the platelet gel group (statistically significant difference). Vogrin et al concluded that platelet-leukocyte gel, applied locally, could improve knee stability in surgery for reconstruction of the ACL[11]. However, as the number of patients of this study is very low, the conclusions must be considered as preliminary.

Magarian *et al,* searched for age dependence in human fibroblasts[12]. Human fibroblasts were obtained from 10 immature and adolescent patients, based on a-priori power calculations, and cultured in a collagen-PRP composite. Three parameters that are pivotal for defect remodeling and wound healing-cell migration, cell proliferation, and scaffold contraction-were chosen as endpoints. Both migration and proliferation were significantly higher in immature cells, but no differences were seen in wound contraction. The findings of this preliminary study suggested that immature patients respond more favorably to treatment with PRP.

Vogrin *et al,* tried to determine if the use of platelet gel (PG) accelerates early graft revascularization after ACL reconstruction in the clinical setting[13]. PG was produced from autologous PRP and applied locally. PG was produced from autologous platelet-rich plasma and applied locally. They quantitatively evaluated the revascularization process in the osteoligamentous interface zone in the bone tunnels and in the intra-articular part of the graft by means of contrast-enhanced magnetic resonance imaging (MRI). After 4-6 weeks, the PG-treated group demonstrated a significantly higher level of vascularization in the osteoligamentous interface than the control group. In the intra-articular part of the graft, they found no evidence of revascularization in either group. Vogrin *et al,* concluded that locally applied PG seems to enhance early revascularization of the graft in the osteoligamentous interface zone after ACL reconstruction.

Vavken and Murray assessed the feasibility of successfully repairing the torn ACL in several large animal models of primary repair of partial and complete ACL transection over 4 to 14 weeks[14]. A bioactive and biocompatible scaffold was developed. This biomaterial showed promising functional, suggesting potential for a successful, future clinical application.

Vavken *et al,* study tested whether the strength of a tissue-engineered ACL repair is associated with VEGF receptors' mRNA expression of ACL cells and whether age influences this association in a porcine model[15]. Nineteen female Yucatan pigs underwent enhanced ACL repair. Biomechanical testing was performed after 15 weeks of healing. Messenger RNA of VEGF receptors 1 and 2 in ACL fibroblasts was assessed by RT-PCR. The ACL structural properties were regressed on receptor expression levels in a multivariate model including serum levels of VEGF, age, and weight as potential confounders. While maximum load and linear stiffness were independent of VEGF receptor expression, VEGF receptor 1 was associated with displacement (positively) and yield load (negatively). In a multivariate model of VEGF receptor expression and biomechanics, age was associated with maximum load and yield load. Vavken *et al,* suggested that high VEGF receptor expression, even more so at higher age, results in a more compliant scar, which in turn may lead to greater knee laxity and a compromised clinical result[15].

According to Mastrangelo, *et al*[16], enhanced primary repair of the ACL using a collagen scaffold loaded with platelets seems to improve the functional healing of suture repair in animal models. In their study, Mastrangelo *et al,* tried to determine if lowering the platelet concentration would reduce the structural properties of the repaired ACL and increase postoperative knee laxity[16]. Eight Yucatan mini-pigs underwent bilateral suture repair. In one knee, the repair was augmented with a collagen scaffold saturated with platelet-rich plasma (PRP) containing five times the systemic baseline of platelets (5×) while the contralateral knee had a collagen scaffold saturated with PRP containing three times the systemic baseline of platelets (3×). After 13 weeks of healing, knee joint laxity and the struc-

tural properties of the ACL were measured. The 3× platelet concentration resulted in a 24.1% decrease in cellular density of the repair tissue, but did not significantly decrease the structural properties for the yield load and linear stiffness, respectively]. The 3× platelet concentration also did not significantly change the mean anteroposterior knee laxity at 30° and 90° of flexion but did result in a lower AP laxity at 60°. The main conclusion of that animal experiment was that the decrease in platelet concentration from 5× to 3× to enhance suture repair of the ACL did not significantly harm the mechanical outcomes.

In a prospective randomized controlled clinical study, Cervellin *et al,* evaluated whether PRP was able to reduce the anterior knee pain, the kneeling pain, and donor-site morbidity[17]. In other words, they evaluated whether platelet-rich plasma (PRP), due to its anti-inflammatory properties and capacity to stimulate tissue regeneration, was able to reduce the anterior knee pain, the kneeling pain, and donor-site morbidity. Forty young athletes with the indication of ACL reconstruction with patellar tendon grafts were randomly assigned to group A (n = 20 patients, control group) or group B (n = 20 patients, PRP group). The autologous PRP gel was applied to both the patellar and tendon bone plug harvest site and stabilized by the peritenon suture. The study showed the usefulness of PRP in reducing subjective pain at the donor-site level after ACL reconstruction with BPTB. However, Cervelli et al stated that this approach deserves further investigations to confirm PRP efficacy and to elucidate its mechanism of action.

MENISCAL DEFECTS

Ishida *et al,* tested the hypothesis that PRP enhances meniscal tissue regeneration in vitro (monolayer meniscal cell cultures) and in vivo (rabbit meniscus)[18]. The findings of their study suggested that PRP seems to enhance the healing of meniscal defects. Zellner *et al,* examined the role of MSCs in meniscal tissue repair in a rabbit model[19]. Circular meniscal punch defects (2 mm) were created in the avascular zone of rabbit menisci and left empty or filled with hyaluronan-collagen composite matrices without cells, loaded with platelet-rich plasma, autologous bone marrow, or autologous mesenchymal stem cells. The study showed the necessity of MSCs for the repair of meniscal defects in the avascular zone. MSCs seemed to fulfill additional repair qualities besides the delivery of growth factors. In a review article Shybut and Strauss stated that for complex, recurrent, or avascular zone tears, particularly when surgery is limited to meniscal work, consideration can be given to augmenting the repair with a fibrin clot or PRP[20]. However, it was just an opinion of the authors, not based in scientific evidence.

JUMPER´S KNEE (PATELLAR TENDINOPATHY)

Kon *et al,* described a minimally invasive way to apply PRP growth factors to chronic patellar tendinopathy in male athletes[21]. Twenty male athletes with a mean history of 20.7 months of pain received treatment, and outcomes were prospectively evaluated at 6 months follow-up. No severe adverse events were observed, and statistically significant improvements in all scores were recorded. The results of this preliminary study suggested that the method could be safely used for the treatment of jumper's knee, by aiding the regeneration of tissue which otherwise has low healing potential. Filardo et al evaluated the efficacy of multiple PRP injections on the healing of chronic refractory patellar tendinopathy after previous classical treatments have failed[22]. They treated 15 patients affected by chronic jumper's knee, who had failed previous nonsurgical or surgical treatments, with multiple PRP injections and physiotherapy. They also compared the clinical outcome with a homogeneous group of 16 patients primarily treated exclusively with the physiotherapy approach. The clinical results of this retrospective study were encouraging, indicating that PRP injections could have the potential to promote the achievement of a satisfactory clinical outcome, even in difficult cases with chronic refractory tendinopathy after previous classical treatments have failed.

RESUMEN

El plasma rico en plaquetas (PRP) se está utilizando cada vez más. Usando como palabras clave "PRP" y "knee" (rodilla) se hizo una búsqueda en PubMed sobre el uso del PRP en las lesiones deportivas de la rodilla. Se encontraron 22 artículos. Muchos de ellos fueron estudios realizados en animales y el resto estudios sin grupo control llevados a cabo en humanos y publicados en revistas de rigor científico modesto. Dichos estudios animales y humanos sugieren que la colocación de un andamio en puente de colágeno-PRP en el defecto central del LCA podría estimular biomecánicamente e histológicamente su cicatrización. También que las inyecciones intra-articulares de PRP podrían mejorar la cicatrización de defectos meniscales. Por último, que las inyecciones de PRP podrían promover resultados satisfactorios en casos de rodilla de saltador (tendinitis rotuliana). Teniendo en cuenta la baja calidad de los datos publicados en la bibliografía y tras realizar una valoración objetiva del valor del PRP en las indicaciones previamente mencionadas, mi conclusión es que el PRP es todavía es un tratamiento experimental, que en muchos casos no ha demostrado tener un valor significativo en cuanto a sus efectos.

Palabras clave: PRP (plasma rico en plaquetas). Lesiones deportivas. Rodilla.

SUMMARY

The use of platelet-rich plasma (PRP) is becoming increasingly available. PubMed articles related to the use of PRP in sports injuries of the knee were searched using the following key words: PRP and knee. A total of 22 reports were found. Many of them were animal studies and the rest were human clinical studies with no controls and published in journals that do not expect as much rigour in the scientific validity. The aforementioned animal experiments and clinical studies suggest that placement of a collagen-PRP bridging scaffold in a central ACL defect can stimulate healing of the ACL histologically and biomechanically. Also that intra-articular injections of PRP can enhance the healing of meniscal defects. Finally, that PRP injections can have the potential to promote the achievement of a satisfactory clinical outcome in cases of jumper´s knee (patellar tendinopathy). Taking into account the low quality of the data reported in the literature and after performing an objective view of the value of PRP for the various indications, my conclusion is that PRP is a treatment that is still experimental and in many instances shown to be not significant in its effects.

Key words: Platelet-rich plasma (PRP). Sports injuries. Knee.

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