Platelet rich plasma: what should the rheumatologist expect?

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ABSTRACT

In the last few decades, thousands of patients have benefited from platelet rich plasma (PRP) therapies, emerging as a safe alternative in many different medical fields. Current evidence suggests that PRP may be of benefit over standard treatment in osteoarthritis patients. Also, in the musculoskeletal soft tissue injuries potential healing effects are waiting to be confirmed with robust evidence. Finally, in systemic rheumatic diseases PRP seems to have a role to play in the treatment of extra-articular symptoms.

Keywords: Rheumatology; Platelet rich plasma

INTRODUCTION

In the past few decades, the versatility, safety and biocompatibility of platelet rich plasma (PRP) has stimulated its therapeutic use in many different medical fields, including orthopaedics[1], sports medicine[2], ophthalmology[3], stomatology[4], dermatology[5] and plastic surgery[6]. Although there is no consensus about PRP definition[7], it can be described as a blood derived product characterized by a platelet concentration that is higher than the concentration of the original blood collected[8]. Degranulation of those platelets causes the release of various growth factors and cytokines, which play a crucial role in the healing process[9,10]. In fact, clinical studies performed in different medical areas revealed various processes, including haemostasis, inflammation, angiogenesis and tissue anabolism, modulated by the molecular pool contained in PRP[9].

PRP is harvested from patient's peripheral blood and centrifuged to obtain a highly concentrated sample of platelets. This step separates the blood into 3 different layers, as determined by the density gradient: the lower layer, composed by red blood cells; the middle layer, composed mainly by white blood cells; and an upper layer composed by plasma. The upper layer can be divided in 3 fractions depending on the amount of platelets present, with an increase gradient from the bottom to the lower fraction, allowing the clinical use of the fraction with the higher concentration of platelets. The next step, depending on the protocol, consists on separation of each fraction into different sterile tubes. Before application to the site of injury, the product is activated to induce the release of platelet growth factors and other bioactive molecules. Finally, depending on the desired application mode, injected or gel, the activated mixture is injected few minutes after activation or is applied later, after being transformed in a platelet gel[7].

The purpose of this review is to summarize the existing evidence on the role of PRP in different rheumatic pathologies.

For this end, a systematic search up to January of 2015 was conducted in MEDLINE (via PubMed) to identify relevant articles. Search terms included "platelet rich plasma" or "PRP" combined with "Osteoarthritis", "musculoskeletal soft tissue injuries", "Rotator cuff tendinopathy", "rotator cuff partial rupture", "lateral epicondylitis", "plantar fasciopathy", "achilles tendinopathy", "vasculitis", "Sjögren's syndrome", "systemic lupus erythematous", "systemic sclerosis", "rheumatoid arthritis" or "spondilartrophaties". Additional relevant references cited in retrieved articles were also evaluated.

Osteoarthritis (OA)

Osteoarthritis is a whole joint disease characterized by degradation and loss of articular cartilage, hypertrophic bone changes with osteophyte formation, subchondral bone remodelling, and inflammation of the synovial membrane[11]. The burden of disease includes pain, ac-

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tivity limitations and markedly reduced quality of life[12]. The prevalence of knee OA in the Portuguese population has been estimated to be 12.4%, according the *Epireuma* national survey[13].

PRP AND KNEE OA

Studies on the application of PRP in the knee OA were first published in 2008 by Sánchez M *et al.*, whom described an observational retrospective cohort study based on three weekly PRP injections compared with hyaluronic acid (HA) injections. This preliminary information about the effectiveness of intra-articular injections of PRP showed success rates by week 5 for the pain subscale, physical function subscale and overall Western Ontario and McMaster Universities Arthritis Index (WOMAC)[14].

Since then many studies have been published. However, randomized controlled trials and homogeneity regarding PRP preparation, follow-up duration, functional outcome and subject's pathology characteristics have been lacking. A recent published meta-analysis, which explored the effectiveness of PRP in the treatment of knee cartilage degenerative pathology, including 16 studies, with a total enrolment of 1543 patients, showed a significant functional improvement from basal injection and a continual efficacy for at least 12 months[15]. Furthermore, in two-years follow-up studies, the beneficial effect remained above the pre-treatment value, in spite of the declining of the scores at the final follow-up[16,17].

When compared with patients receiving HA, those in the PRP group exhibited better and prolonged beneficial effects[15]. To our knowledge the use of saline as a placebo control has only been used in one trial. Patel *et al*. published a double-blinded, randomized, placebo-controlled trial, which included 78 patients (156 knees) with symptomatic early OA, documenting statistically significant improvement in all WOMAC parameters in the PRP group, within 2 to 3 weeks, and lasting until the 6 months of follow-up. Although a slight worsening at the 6-month follow up was documented, the WOMAC parameters were still better than those at the baseline. In the placebo control group the trend was of worsening scores at all follow-ups compared with baseline[18]. Another randomized controlled trial, aiming to determine the effects of PRP on pain, stiffness, function and quality of life on patients suffering from knee osteoarthritis, compared the PRP treatment with a control group, where only exercise and acetaminophen 500 mg were prescribed, documenting mean changes of total WOMAC, physical component summary and mental component summary of Short Form-36, with the PRP group showing better improvement than the control group (P<0.05). This trial documented that intra-articular PRP knee injection combined with therapeutic exercise can be more effective in pain reduction, improvement of stiffness and quality of life, compared with therapeutic exercise alone[19].

PRP vs HA

When a comparison was made between HA and PRP treatments in intra-articular infiltration of knee OA, both treatments resulted in clinical improvement but a trend favourable for PRP was shown[20–24]. Furthermore, although it appears that these better results with PRP occur in younger patients with less advanced degenerative lesions[21], the superiority of the PRP may also exist in more advanced OA[23].

Patient's selection

Regarding patients selection, the degenerative chondropathy (Kellgren-Lawrence grade 0) group had the highest effect, followed by the early OA group (grade 1 and 2) and the advanced OA group (grade 3 and 4)[15]. These results are compatible with those of most trials, favouring discriminative usage of PRP in cases with degenerative chondropathy and mild OA.

PRP preparation and application

Regarding the PRP preparation and application, the number of injections ≤2, the use of single spinning approach, and lack of activation agents led to an uncertainty of the treatment effectiveness in Chang *et al*. meta-analysis[15]. In fact, there has been no homogeneity in the number of infiltrations per cycle or the time between those infiltrations. One to four injections, with an interval of 1 to 4 weeks, have been used in the different protocols published. Because the inflammatory process and patient's symptoms usually subside in two weeks, some authors defend a 2 weeks or more interval between infiltrations[19]. Finally, Patel *et al*. showed no difference between single injection *versus* 2 injections of PRP (with a 3 weeks interval)[18].

The difficulty in this research field is multiplied by the numerous products/protocols used. In fact, different methods lead to the production of different concentrates; which may present different properties and lead to different clinical results. Filardo *et al.* trial included 144 symptomatic patients affected by cartilage

degenerative lesions and OA, to explore two preparations approaches, single versus double-spinning procedures. The single spinning – Platelet Rich Growth Factor (PRGF), consisted of 4 tubes of 9 ml of blood centrifuged at 580g for 8 min, and the procedure was repeated for every injection. In the double spinning approach two centrifugations (the first at 1,800 rpm, for 15 min, to separate erythrocytes, and a second at 3,500 rpm, for 10 min, to concentrate platelets) produced a unit of 20 ml of PRP, which were divided in 4 units of 5 ml. One unit was used for the first injection within 2 h, the other 2 units were stored at -30°C and used for the second and third treatments, first thawed in a dry-thermostat at 37°C for 30 min just before application, and the forth unit was sent to the laboratory for quality analysis (platelet count and bacteriological test). The author showed that both groups presented a similar improvement in all the scores evaluated at all the follow-up times[25]. Finally, Gobbi *et al.*, explored the hypothesis that three intra-articular PRP injections at monthly intervals, repeated annually, would improve the outcome at the final follow-up when compared to a group in whom the treatment was not repeated. They showed that the beneficial effects of the treatment remained above the pre-treatment value, although it declined with time in both groups. Patients with two cycles have showed higher mean values for all the scores[16].

Structural outcome

In a prospective study, with a small sample of 22 patients, and no control group, Halpern *et al.*, studied magnetic resonance imaging (MRI) outcome after PRP treatment for early knee OA, in a 1-year follow-up. Qualitative MRI evaluation demonstrated no changes per compartment, in at least 73% of the cases, in the final follow-up[26]. This results contrast with those that suggest an annual decrease of cartilage volume in knee OA compartments[27].

Adverse events

No major adverse events or complications have been reported in knee OA patients treated with PRP. Thought, temporary mild worsening of pain in the knee joint after application of PRP has been documented, with a spontaneous resolution in a few days[15].

PRP AND HIP OA

There are only few trials concerning the use of PRP in hip OA. In 2011, Sanchez *et al.* published a pragmatic and preliminary study assessing the safety and potential value of PRP treatment of hip OA. They used ultrasound-guided PRP injections, and preformed 3 injections with an interval range from 1 to 2 weeks. Results showed clinically significant reductions in pain and function in patients with severe hip OA up to 6 months post-treatment. Side effects were limited to a sensation of heaviness in the injection site[28]. Furthermore, in 2013, Battaglia *et al.* published the first prospective, comparative, randomized, single-blinded trial assessing the efficacy of ultrasound-guided intra-articular injection of PRP compared with HA, in symptomatic patients with hip OA not responding to other type of oral therapies. A functional improvement and pain reduction was detected in both groups of patients, with the highest peak between 1 and 3 month follow-up, followed by a slightly progressive worsening between 6 and 12 month. However, in both groups the final scores remained higher than baseline, with no significant differences between the two groups[29].

PRP AND MUSCULOSKELETAL SOFT TISSUE INJURIES

The use of PRP is increasing in the treatment of musculoskeletal soft tissue injuries such as ligament, muscle and tendon tears and tendinopathies. In a Cochrane review, with the objective to assess the effect of platelet-rich therapies for treating musculoskeletal soft tissue injuries, eight clinical conditions were covered: rotator cuff tears (arthroscopic repair); shoulder impingement syndrome surgery; elbow epicondylitis; anterior cruciate ligament (ACL) reconstruction, ACL reconstruction (donor graft site application), patellar tendinopathy, Achilles tendinopathy and acute Achilles rupture surgical repair. The authors concluded that for the individual clinical conditions, there is currently insufficient evidence to support the use of PRP for treating musculoskeletal soft tissue injuries and that there is very low quality evidence from the subset of those trials[30].

TENDINOPATHY (RCT) AND PARTIAL RUPTURE OF ROTATOR CUFF

The prevalence of rotator cuff disorders, and the recognized difficulty in achieving rotator cuff healing, has led to high interest in the use of PRP. Results of current studies are not conclusive and may lead to controversy. In a double-blind, placebo-controlled randomized clinical trial, Kesikburun *et al.* included 40 patients

with an history of shoulder pain for >3 months, with the aim to investigate the effect of PRP injections on pain and shoulder functions, in patients with chronic RCT on a standard exercise program. The injections were ultrasound-guided in subacromial space directly into the rotator cuff tendon. The solution, administrated in covered syringes, was injected into the centre of the lesion and 4 sites around the lesion through 1 skin portal. The authors reported that a single injection of PRP was not superior to saline injection in the treatment of chronic RCT and, although effective in improving quality of life, pain, disability, and shoulder range of motion, at 1-year of follow-up, this improvement did not differ from that seen in the placebo group[31]. Still, Rha *et al.* showed that PRP injections provided more symptomatic relief and functional improvement than dry needling at six-month follow-up in supraspinatus tendon lesion (tendinosis or a partial tear less than 1.0 cm, but not a complete tear). However, improvement in the range of motion of the shoulder was not different between the PRP and dry needling groups[32]. Finally, a small sample study, with no control group, reported a safe, significant, sustained improvement in pain, function, and MRI effect for a single injection of PRP under ultrasound guidance, for refractory rotator cuff tendinopathy[33].

Previous studies on the effects of PRP suffer from a lack of standardization, which results in inter-study differences in platelet concentration, activation, and WBC contamination level, factors that can affect the concentrations and the release kinetics of growth factors, which make it difficult to compare study results and can explain contradictory results.

In laboratory studies, Muto *et al.,* reported that exposure to triamcinolone acetonide significantly decreased cell viability and caused cell apoptosis, and these deleterious effects were prevented by the administration of PRP on human rotator cuff-derived cells[34]. PRP seems to promote the proliferation of tenocytes from human rotator cuff tendons with degenerative tears and enhances the gene expression and the synthesis of tendon matrix[35]. Furthermore, according to Sadoghi *et al*. study, PRP has a significant effect on fibroblast proliferation of the human rotator cuff *in vitro*, and the dosage of PRP has significant impact on this influence[36].

Thus, further studies regarding the use of PRP in cuff rotator healing are required. They should focus on the correct PRP preparation and subject's characteristics. In fact, clinical results might be significantly influenced by the patients' age, as both factors, the biological response of the supraspinatus tendon and the growth factors' potential effect, might be jeopardized in the elderly. Furthermore, the specificity of the pathology with indication for this regenerative treatment should be documented.

LATERAL EPICONDYLITIS (LE)

LE appears to be a degenerative process that results from repetitive microtrauma. Samples from the affected tissue demonstrate angiofibroblastic hyperplasia at the extensor origin of the forearm. It is generally self-limiting, and most cases require no more than treatment with simple analgesia. For patients with severe or persistent symptoms a number of different treatments are available. Although, non-surgical approaches to treat LE are numerous, there is no conclusive evidence showing superiority of one method of non-surgical treatment over another[37].

The current evidence suggests that PRP may be of benefit over standard treatment in chronic LE[38,39] and, its effects seem to persist even after a 2 years follow-up[40]. Furthermore, a pilot study suggested that, after 3 ml PRP single injection, there is a trend for increased vascularity at the myotendinous junction up to 6 months, which may precede improved tendon morphology[41].

In previous studies, aiming to compare PRP *versus* corticosteroid, results documented that PRP reduces pain and increases function significantly, exceeding the effect of corticosteroid injection[40,42]. Furthermore, in a double-blinded, prospective, multi-center, randomized trial, 230 patients with chronic LE were included; all patients had at least 3 months of symptoms and failed conventional therapy. After local anaesthetic, the patients had their extensor tendons needled injected with 2 to 3 mL of PRP (active treatment), or 2 to 3 mL of bupivacaine (active control) using the same peppering technique. At 12 weeks, patient outcomes did not found significant differences. At 24 weeks, however, clinically meaningful improvements, regarding pain scores, local tenderness and success rates (defined by 50% or more improvement in pain scores) were found in patients treated with leukocyte-enriched PRP, in comparison with an active control group[43].

PRP is compared with autologous blood injection (ABI) in two trials. In Thanasas *et al.* trial, PRP seems to be superior to ABI in short-term period[44]. Meanwhile, Creaney *et al.* observed a 66% success rate in the PRP group versus 72% in the ABI group, with no statis-

tic difference, at 6 month of follow up. As the authors warn, we should be cautious in interpreting these results, which may be biased by a higher proportion of patients treated with ABI referred for surgery, with consequent increase in mean scores of success rate in the remaining patients in this group.

Finally, in a randomized controlled trial, Krogh *et al.* compared blinded injection of PRP, saline, or glucocorticoid, in 60 patients with chronic LE requiring ultrasonography confirmation of tendinopathy, with a colour Doppler assessed at baseline. Pain reduction at 3 months was observed in all 3 groups, with no statistically significant difference between the groups. However, at 3 months of follow-up, glucocorticoid was more effective than PRP and saline in reducing colour Doppler activity and tendon thickness[45].

ACHILLES TENDINOPATHY (AT)

AT is a chronic, non-inflammatory, degenerative process of the tendon that is manifested by pain, swelling and impaired load bearing capacity. It is a common pathology in those who partake in sporting activities, and an increasing problem in less-active individuals[46]. Although there are many options regarding conservative treatment for AT, non-operative management is ineffective in roughly 25% of patients[47].

In recent years, regenerative medicine has provided a new perspective on the management of chronic AT by delivering growth factors in an attempt to initiate tissue healing. de Vos *et al.* in a randomized, double blind, placebo-controlled trial, included 54 patients with chronic midportion AT, treated with PRP or saline injection. Through each puncture location, five small depots were left at several sites in the degenerative areas of the tendon. This study did not showed greater improvement in pain and activity when compared with saline injections among patients with chronic midportion AT treated with an eccentric exercise program[48]. In a complementary study no improvement in tendon structure and no effect on neovascularisation were observed with the addition of PRP to eccentric exercises[49]. Similar results were obtained by Jonge *et al.* trial, in which PRP injection, in addition to eccentric exercises, did not result in clinical improvement and/or improved structural reorganization on ultrasound after 1 year in chronic mid-portion AT, compared with placebo injection[50]. Contrasting results were showed in two prospective longitudinal case series in which PRP injection successfully treated severe chronic AT[51,52]. Finally, a small retrospective study found modest clinical improvement post-injection, but there was no significant improvement in the MRI appearance of the Achilles tendon post-injection[53].

PLANTAR FASCIOPATHY (PF)

PF is the most common cause of plantar heel pain[54]. Patients typically report a gradual onset of pain in the inferior heel that is usually worse with their first steps in the morning or after a period of inactivity[55]. Spontaneous resolution of symptoms occurs in approximately 80% of patients within 12 month[56]. Conventional non-invasive treatment options include: plantar fascia, gastrocnemius, and soleus stretching, customized orthotics, night splints, extracorporeal shock wave therapy (ESWT), and pain medications[57]. Despite early intervention, approximately 10% of patients fail to improve with conservative management and face chronic heel pain[57]. Invasive strategies, for example, corticosteroid injections, and percutaneous, endoscopic, or open fasciotomy have been used in refractory cases with varying results[55].

As in other fields, PRP use is based on the believe that it might provide cellular and humoral mediators that enhance tissue healing, though plantar fascia could enable the healing necessary to reverse the degenerative process, given the pathologic nature of chronic recalcitrant PF is angiofibroblastic hyperplasia with degeneration at the origin of the proximal plantar fascia[58].

Most of the studies assessing the use of PRP in patients with chronic PF, previously refractory to conservative management, have shown improvement in symptoms between baseline and last follow-up assessment[58–66]. Nevertheless, in a randomized trial, with 54 subjects with unilateral chronic PF and more than 4 months of symptoms, divided in 3 groups (autologous conditioned plasma (ACP) and conventional treatment, ESWT and conventional treatment, and conventional treatment alone), the authors documented that either ACP or ESWT resulted in modestly improved pain and functional scores compared with conventional treatments alone, over a 6-month follow-up period. All the groups demonstrated improvements in plantar fascia thickness from baseline to the end of the evaluation period. However, the median ultrasound plantar fascia thickness improvement in the ACP group at the 6-month of follow-up was 1.3 mm, compared with the ESWT and conventional treatment groups, which both showed improvements of 0.6 mm at 6 months[66].

Furthermore, when Ak ahin *et al.* compared the PRP efficacy versus corticosteroid injection treatment for

chronic PF, results revealed that both methods were effective and successful in treating PF[60]. In contrast, other studies have suggested that PRP is more effective[59,65] and durable[65] than cortisone injection for the treatment of chronic recalcitrant cases of PF. Finally, Kim *et al.* compared PRP with dextrose prolotherapy (DP), which consists in the use of concentrated dextrose as an irritant to stimulate a mild inflammation. Both treatments appeared effective and no significant differences were observed, however PRP treatment resulted in a better initial improvement in function when compared with DP[58].

Currently, there is no consensus about PRP application and preparation, and its use in PF is no exception. The total PRP volume injected varied between 2.5 and 5 ml in the studies regarding PF[58–66]. In Kumar *et al.* report, after injecting only 1.5 ml to each heel in three patients with bilateral PF, no improvement was notice. Consequently, further bilateral injections with the full amount of PRP (3 ml) were administered with success[66]. The number of injections ranged from 1 to 3, in different weeks. No activator has been used and leukocytes reduction was not performed. The rationale for PRP preparation containing WBC was their capacity to generate an antibacterial response, to debride dead tendon tissue and jump-start healing, and because they also produce growth factors[58]. However, whether each variable in PRP preparation has a positive effect on PF, it's not known, because no comparative data has been published to date. No complication or adverse effect related to PRP administration was recorded in those studies.

OTHER RHEUMATIC CONDITIONS

Unlike other treatment modalities, PRP and its healing effects offers the unique potential for tissue regeneration at the cellular level with a favourable side effect profile. Thus, it is expected that its use expand to other areas of rheumatology.

In fact, PRP seems to be effective and safe in increasing lacrimal production and improving ocular staining secondary to severe dry eye[67]. It has also been described that activated PRP stimulates the proliferation of human dermal papilla cells, increases the survival of hair follicle cells through its anti-apoptotic effect on dermal papilla cells, and may stimulate hair growth by prolonging the anagen phase of the hair cycle[68]. Interestingly, in a two case report, Kanemaru *et al.* published for the first time the use of PRP in skin ulcers in patients with systemic sclerosis (SSc). One of the patients suffered from an ulcer, refractory to conservative therapies, on the left-middle finger for 1 year. She was treated with PRP after MRI have excluded osteomyelitis, and within one month of follow-up the skin defect was practically resolved, suggesting that PRP may have a place in the treatment of cutaneous ulcers in SSc[69]. Furthermore, aiming to investigate the anti-inflammatory effect of PRP, Lippross *et al.* demonstrated that PRP could attenuate arthritic changes, as assessed histologically and based on protein synthesis of typical inflammatory mediators in the synovial membrane and cartilage, in a porcine model of rheumatoid arthritis[70].

This data suggest that PRP may play a role in the treatment of extra-articular symptoms in systemic rheumatic diseases like vasculitis, Sjögren's syndrome, systemic lupus erythematous, SSc, rheumatoid arthritis or spondilartrophaties, among others. Further studies are required.

CONCLUSION

Thousands of patients have benefited from PRP therapies, emerging as safe alternative for many diseases, but limited robust evidence of efficacy still remains a problem. As it was demonstrated by Magalon J *et al.,* whom compared the biological characteristics of PRP obtained from 4 medical devices using a single donor, different PRP preparations resulted in significant differences regarding red blood cells, white blood cells, platelets and growth factors concentrations in the final product[71]. This could explain the large variability in the clinical benefit of PRP reported in the literature. Such differences have been explained by the heterogeneity of preparation techniques (frequency, speed and length of the centrifugation; the use of an anticoagulant that does not affect platelet functions[72], the presence or absence of leukocytes, the use of an activator, final platelet concentration) and administration technique (volume, frequency and delivery means of administration). Furthermore, post-administration rehabilitation, participant's characteristics and disease severity, also seem to contribute for the difficulty to compare the studies published. Therefore, further standardized research on PRP is needed to assess the benefits and, especially, to understand its mechanism of action. In Rheumatology much should be done, to in-

vestigate the potential areas in which PRP can bring symptomatic and structural healing.

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