Foot and Ankle Surgery 20 (2014) 2–9

Contents lists available at ScienceDirect

Foot and Ankle Surgery

journal homepage: www.elsevier.com/locate/fas

Review

Platelet-rich plasma for foot and ankle pathologies: A systematic review

F. Vannini [a], B. Di Matteo [b,*], G. Filardo [b], E. Kon [b], M. Marcacci [b], S. Giannini [a]

[a] I Orthopaedic Clinic and Movement Analysis Laboratory, Rizzoli Orthopaedic Institute, Via di Barbiano n. 1/10, 40136 Bologna, Italy
[b] II Orthopaedic Clinic and Biomechanics Laboratory, Rizzoli Orthopaedic Institute, Via di Barbiano n. 1/10, 40136 Bologna, Italy

ARTICLE INFO

Article history:
Received 18 October 2012
Received in revised form 2 August 2013
Accepted 7 August 2013

Keywords:
Platelet-rich plasma
Tissue regeneration
Growth factors
Biological enhancers
Foot and ankle

ABSTRACT

Background: The aim of this article is to review systematically all the literature available on the clinical application of PRP for the treatment of foot and ankle pathologies, to understand its potential and best indications for clinical use.
Methods: A systematic search of the PubMed database was performed. Research criteria were the following: (1) papers in the English language, (2) dealing with the clinical application of PRP for the treatment of orthopedic-related conditions affecting the foot and ankle district, (3) with I to IV level of evidence, and (4) reporting clinical results.
Results: A total of 17 studies fulfilled the inclusion criteria. Nine papers dealt with Achilles tendon management, 2 articles with plantar fasciitis, 3 papers with talar osteochondral lesions, 2 with PRP application in total ankle replacement, and 1 article with PRP in foot and ankle fusions. The overall evaluation of the results reported does not clearly demonstrate the potential of PRP treatment in any of the specific fields of application.
Conclusions: Considering the literature currently available, no clear indications for using PRP in the foot and ankle district emerged.
Level of evidence: Level IV, systematic review of Level I, II, III and IV studies.

Contents

1. Introduction

The attractive prospective of applying biological enhancers for the treatment of musculoskeletal diseases is one of the hottest topics both for basic researchers and orthopedic clinicians worldwide. In particular, the orthopedic practitioner is always on the lookout for autologous bio-adjuvants as a new option to treat a wide range of clinical conditions [1]. They can be used as a conservative strategy but also as an enhancer during classical surgical procedures. The purpose, in both cases, is to stimulate the regeneration of tissues otherwise characterized by a low intrinsic healing potential [2,3]. Furthermore, both physicians and patients welcome this biological approach because of its autologous nature, thus avoiding side effects and reactions generally linked to

* Corresponding author at: II Orthopaedic Clinic and Biomechanics Laboratory, Rizzoli Orthopaedic Institute, Via di Barbiano n. 1/10, 40136 Bologna, Italy.
Tel.: +39 051 6366567; fax: +39 051 583789.
E-mail address: berardo.dimatteo@gmail.com (B. Di Matteo).

1268-7731/$ – see front matter
http://dx.doi.org/10.1016/j.fas.2013.08.001

"industrial" drugs. Among these biological solutions [4], Platelet-rich Plasma (PRP) is the most common way to promote tissue regeneration: its clinical application in musculoskeletal diseases has been increasing constantly over the last years, and several studies have been published on this topic [5].

PRP is an autologous concentrate of platelets and therefore platelet-derived growth factors (GFs) and other molecules, obtained directly from the peripheral venous blood of the patient. Platelets contain storage pools of GFs including platelet-derived growth factor (PDGF), transforming growth factor (TGF-β), platelet-derived epidermal growth factor (PDEGF), vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1), fibroblastic growth factor (FGF), and epidermal growth factor (EGF) [6]. Alpha granules are also a source of cytokines, chemokines and many other proteins [6,7] variously involved in stimulating chemotaxis, cell proliferation and maturation, modulating inflammatory molecules and attracting leukocytes [5,6]. Besides alpha granules, platelets also contain dense granules, which store ADP, ATP, calcium ions, histamine, serotonin and dopamine, thus also playing a complex role in tissue modulation and regeneration [6]. Finally, platelets contain lysosomal granules which can secrete acid hydrolases, cathepsin D and E, elastases and lysozyme [7,8], and most likely other not yet well characterized molecules, the role of which in tissue healing should not be underestimated. Several in vitro and in vivo animal studies showed the potential beneficial effect of PRP in promoting cellular anabolism and regeneration of various tissues, including bone, cartilage and tendons.

In view of the above, PRP might also represent an important treatment option for surgeons and physicians dealing with foot and ankle pathologies [9–11].

However, despite its wide clinical application supported by the enthusiasm for this biological approach, it is not clear to what extent the use of PRP is supported by real scientific evidence.

The purpose of this article is to review systematically all the literature available on the clinical application of PRP for the treatment of foot and ankle pathologies, to understand its potential and the best indications for clinical use.

2. Materials and methods

A systematic research of the PubMed database was performed. The research criteria were the following: (1) papers in the English language, (2) dealing with the clinical application of PRP for the treatment of orthopedic-related conditions affecting the foot and ankle district, (3) with a I to IV level of evidence, and (4) reporting clinical results. Both conservative and surgical applications of PRP were considered for the review.

For this purpose, a research formula was used. All articles containing the words "platelet rich plasma" or "platelet gel" or "platelet concentrate" or "platelet-derived growth factors" combined with the words "foot" or "ankle" or "Achilles tendon" or "fasciitis" were identified. This search produced 194 papers in total. Reviews, in vitro and animal studies and also papers dealing with non orthopedic conditions were excluded. At the end of this selection, 14 papers were considered eligible and the references of each paper were analyzed to further identify any other articles that could be taken into consideration for the present study. Reviews and especially their references were also analyzed to ensure that each clinical paper was included in this systematic review. At the end of the process, 17 papers fulfilled the selection criteria (Table 1).

3. PRP for achilles pathologies

The Achilles tendon is the most common site for PRP application, due to the large prevalence of Achilles tendon diseases caused by the increasing practice of sport in all age groups.

Platelet concentrates have been used in the management of Achilles tendon pathologies, both conservatively and as a biological enhancer during surgical procedures.

In 2007 Sánchez et al. first published a retrospective study [12] where 6 patients, treated with open suture repair and platelet concentrate, were retrospectively compared with a matching group of 6 patients treated with the same open suture technique alone. The intra-operative use of PRP consisted of covering the sutured tendon with an autologous platelet rich fibrin matrix combined with a subcutaneous injection of 4 ml PRP before suturing the skin.

All the patients were studied using ultrasonography and follow-up evaluation consisted of measuring the time necessary to recover a full range of motion of the ankle, time to return to gentle running, and time to return to training. Results showed better performance in all the parameters for the group treated with the combination of suturing and PRP. Long-term ultrasound examination showed an increase in cross-sectional area of the Achilles tendon in both groups but the PRP group had a significantly higher increase compared to the control group.

Contrasting results were reported by a randomized controlled trial performed by Schepull et al. [13]. Thirty patients affected by Achilles tendon rupture requiring surgical repair were assigned to two different treatment groups, the first one consisting of tendon suture alone and the second one combining suture with an intra-operative injection of 10 ml autologous PRP. The patients were evaluated by biomechanical tests and clinical scores for up to 52 weeks of follow-up. Objective measurements tested elastic modulus, strain per force, heel raise index and transverse area of the repaired tendon, whereas the clinical score adopted was the Achilles Tendon Rupture Score (ATRS). At 1 year follow-up the authors did not find any statistical inter-group difference in the biomechanical parameters examined and the PRP group totalized a significantly lower ATRS. In light of these data, the authors concluded that PRP supplementation does not provide any clinical beneficial effect in Achilles tendon healing after surgical repair, but might actually even be detrimental for the clinical outcome.

Concerning the conservative management of Achilles partial tendon rupture, a case report [14] has been described. A 34-year old basketball player affected by a partial Achilles tear was treated with 3 intra-tendineous injections of 5 ml PRP one week apart, starting from 6 days after the trauma. The athlete was able to return to sport 64 days after the original trauma, and 75 days were needed to return to a full game. MRI and ultrasonography performed before and after the treatment showed a marked improvement in tendon signal and in tissue structure.

The most debated study on the application of PRP in Achilles tendon pathology is a randomized controlled trial comparing PRP vs saline injection in patients affected by chronic mid-portion Achilles tendinopathy [15]. Fifty-four patients, aged from 18 to 70 years, were divided into 2 homogenous groups: the treatment consisted of a single ultrasound-guided injection of 4 ml of non-activated PRP or a single injection of 4 ml of saline solution (control group). After the injection, patients were assigned to a standardized rehabilitation program based on eccentric exercises. Prospective evaluation was performed at 6, 12, and 24 weeks of follow-up using the Victorian Institute of Sport Assessment-Achilles tendon (VISA-A) questionnaire, and registering patient satisfaction and return to sport. The results showed improvement in both groups of patient without any significant difference in outcome between the PRP and the control group. In a later paper [16], the same authors reported the results at 1 year of follow-up confirming no difference in clinical outcome and in time to return to sport. The ultrasonographic evaluation 1 year after treatment showed reduction in neovascularization, reduction of antero-posterior thickness and improvement in overall tendon structure in both groups, without any significant inter-group difference.

Table 1
Synopsis of all the studies on PRP application in foot and ankle pathologies.

Authors, journal and year	Level of evidence	Disease	Application	PRP preparation method	Activation method	Protocol	Combined treatments	Control group	Number of patients	Follow-up	Outcome
Sanchez et al. Am J Sports Med 2007	Case series	Achilles tendon rupture	Surgical	Single centrifugation (PRGF system II – BTI)	Ca-chloride	Intra-op.	Tendon suture	Yes (historical controls)	6	6 months	Better outcome and faster recovery for PRP group
Schepull et al. Am J Sports Med 2011	Randomized trial	Achilles tendon rupture	Surgical	Double centrifugation (laboratory made)	Ca-Chloride	Intra-op. (10 ml PRP)	Tendon suture	Yes (tendon suture alone)	16 PRP vs 14 control	12 months	No significant difference in biomechanical tests; clinical outcome better in the control group
Filardo et al. Orthopedics 2010	Case report	Achilles partial rupture	Conservative	Double centrifugation (laboratory made)	Ca-chloride	3 weekly injections of 5 ml PRP	No	No	1	18 months	Fast return to full pre-injury sport practice
Gaweda et al. Int J Sports Med 2010	Case series	Achilles tendinopathy	Conservative	Single centrifugation (PRP Kit–Curasan)	Not assessed	1 injection of 3 ml PRP	No	No	14	18 months	Significant pain reduction and functional recovery
deVos et al. JAMA 2010 deJonge et al. Am J Sports Med 2011	Randomized trial	Achilles tendinopathy	Conservative	Single centrifugation (Platelet Separation System–Biomet)	No	1 injection of 4 ml PRP	Local anesthesia	Yes	27 PRP vs 27 saline solution	12 months	Clinical improvement for both treatments but no intergroup significant difference
Finoff et al. PM&R 2011	Case series	Achilles, tibialis posterior and plantar tendinopthay	Conservative	Single centrifugation (Magellan Autologous Platelet Separator System–Arteriocyte Medical System- or GPS III Platelet Separation System–Biomet)	No	1 injection of 2.5–3.5 ml PRP	Local anesthesia; US-guided needle tenotomy	No	25 (14 Achilles, 1 tibialis posterior, 9 plantar fasciopathies)	14 months	Positive clinical results but not conclusive sonographic findings
Owens et al. Foot Ankle Int 2011	Case series	Achilles tendinopathy	Conservative	Single centrifugation (Symphony System- DePuy)	Not assessed	1 injection of 6 ml PRP	No	No	10	24 months	Clinical but not MRI improvement
Monto et al. Foot Ankle Int 2012	Case series	Achilles tendinopathy	Conservative	Single centrifugation (Accelerate platelet concentration system–Exactech)	No	1 injection of 4 mL PRP	Local anesthesia	No	30	24 months	Significant clinical improvement in 28 patients
Aksahin et al. Arch Orthop Trauma Surg 2012	Randomized trial	Plantar Fasciitis	Conservative	Double centrifugation (laboratory made)	Not assessed	1 injection of 3 mL PRP	Local anesthesia	Yes (cortico-steroids)	30 PRP vs 30 cortico-steroids	6 months	Clinical improvement in both group without inter-group difference
Ragab et al. Arch Orthop Trauma Surg 2012	Case series	Plantar Fasciitis	Conservative	Double centrifugation (laboratory made)	Not assessed	1 injection of 5 mL PRP	No	No	25	12 months	Clinical and sonographic improvement. 90% pts had full recovery
Giannini et al. Clin Orthop Relat Res 2009	Case series	Osteochondral talar lesions	Surgical	Double centrifugation (laboratory made)	Ca-chloride	Intra-op (1 mL PRP)	Scaffold made of: MSCs + PRP + HA membrane (or collagen powder)	No	48	24 months	Significant improvement in all clinical parameters
Giannini et al. Injury 2010	Comparative study	Osteochondral talar lesions	Surgical	Double centrifugation (laboratory made)	Ca-chloride	Intra-op. (1 mL PRP)	MSCs + PRP + HA membrane (or collagen powder)	Yes (historical controls)	81 (25 MSCs scaffold vs 10 open ACI vs 46 arthroscopic ACI)	24 months	Results comparable to those of arthroscopic ACI with lower costs

Mei-dan et al. Am J Sports Med 2012	Randomized trial	Osteochondral talar lesions	Conservative	Single centrifugation (PRGF system II–BTI)	Not assessed	3 injections of 2 mL PRP 14 days apart each other	No	Yes (HA)	15 PRP vs 15 HA	7 months	Statistically better clinical outcome in PRP group
Barrow et al. Foot Ankle Int 2005	Case series	Tibio-fibular fusion in total ankle replacement	Surgical	Single centrifugation (Symphony PCS system - DePuy)	Not assessed	Intra-op (amount of PRP not specified)	Multiple drilling of tibia and fibula surfaces and final fixation by two cortical screws	No	20	6 months	100% fusion rate at 6 months vs 62% of historical controls
Coetzee et al. Foot Ankle Int 2005	Case series	Tibio-fibular fusion in total ankle replacement	Surgical	Single centrifugation (Symphony PCS system – DePuy)	Not assessed	Intra-op (amount of PRP not specified)	Multiple drilling of tibia and fibula surfaces and final fixation by two cortical screws	Yes (historical controls)	66 PRP vs 114 controls	6 months	Better fusion rate and lower delayed unions or non-unions in PRP group
Bibbo et al. J Surg Orthop Adv 2005	Case series	Foot and ankle fusion in high risk patients	Surgical	Single centrifugation (Symphony I & II platelet concentrating systems–DePuy)	Not assessed	Intra-op (amount of PRP not specified and depending on the defect size)	Internal fixation device according to specific site; bone graft when needed	No	62	12 months	94% union rate within 45 days from surgery. Low complication rate

Gaweda et al. [17] injected PRP in 14 patients (15 tendons in total) with non-insertional Achilles tendinopathy. Follow-up evaluation at 6 weeks, and at 3, 6, and 18 months was performed using AOFAS, VISA-A, and ultrasonographic and power-Doppler examination. A marked and significant increase was recorded in both clinical scores, and ultrasonography revealed normalization of peritendineum, reduction of tendon thickening, and reduction of hypoechoic lesions. After an initial increase up to 3 months of follow-up, power-Doppler showed a reduction in tendon vascularity at the final follow-up.

The clinical efficacy of PRP has been suggested also by research groups led by Finoff and Owens [18,19]. Finoff et al. [18] treated chronic tendinopathy with ultrasound-guided needle tenotomy and PRP injection. The study focused on differently located tendinopathies, both in the upper and lower extremities. In particular, 24 patients were treated in the ankle and foot district (14 Achilles tendons, 1 tibialis posterior tendon and 9 plantar fasciopathies). Mean follow-up evaluation was carried out at 14 months (range: 3.5–25 months) and the investigators found a significant decrease in pain with concomitant functional recovery. No correlation was found between clinical outcome and parameters such as age, BMI, smoking status, tendinopathy location, symptom duration or PRP platelet concentration. Furthermore, patients were evaluated pre- and post-procedure by ultra-sound (US) to assess tendon thickness, presence of intra-tendinous calcifications, echostructure, and grade of neovascularization. Overall US evaluation revealed significant improvement in echostructure and reduction in neovascularity and tendon thickness; however, with regards to the foot and ankle districts, no sub-analysis was performed, except for Achilles tendon thickness, which showed minimal, not significant, changes.

Owens et al. [19] retrospectively reviewed a small cohort of 10 patients, all treated with intra-tendinous PRP injections. Evaluation items included Foot and Ankle Ability Measure (FAAM), Foot and Ankle Ability Measure Sport (FAAM-S) and Short Form Healh Survey (SF-8). An improvement was found in each of these clinical scores but MRI evaluation did not reveal a better radiographic appearance in most tendons treated; they remained similar to pre-treatment conditions.

A recent study by Monto et al. [20] confirmed the positive clinical outcome of the aforementioned papers. The authors treated 30 patients affected by chronic tendinopathy, refractory to at least 6 months of traditional non-operative management. Each patient received a single ultra-sound-guided injection of PRP. Clinical evaluation was carried out using the AOFAS score at 0, 1, 2, 3, 6, 12, and 24 months of follow-up and also MRI/US evaluation was performed 6 months after treatment. Clinical results were positive, with a significant improvement with respect to the first evaluation; this improvement was confirmed up to the final follow-up at 24 months. Even MRI/US control scans revealed signs of tendon healing in 27 out of 29 patients. The rate of return to full occupational activity and sport confirmed the trend revealed by the clinical scores and imaging appearance. Two failures were recorded and, interestingly, both cases were related to calcaneal pathology (insertional calcaneal tendinopathy and severe Haglund deformity): despite a clinical improvement after PRP injection, these patients were still complaining of pain and functional limitations, so surgical treatment was performed.

4. PRP for plantar fasciitis

Recently, two papers have been published on the application of PRP for plantar fasciitis [21,22].

The first one, a double-blind trial, has been authored by Akşahin et al. [21] and compares the efficacy of PRP vs corticosteroids for treating plantar fasciitis in a cohort of 60 patients divided into two

treatment groups. Patients received a single intra-lesional injection of 3 ml of PRP or 2 ml of corticosteroids and, in both cases, a local anesthetic was used. After the treatment, patients were evaluated up to 6 months of follow-up. Both treatment groups revealed a significant improvement in terms of functional status and pain at final evaluation, without any significant inter-group difference. Investigators concluded that PRP provided good clinical results and, even if not superior to corticosteroids, it could be applied as a first line injective approach in order to avoid the well-known potential risks of corticosteroids.

The second paper by Ragab and Othman [22] described the clinical outcome in 25 patients treated by a single injection of 5 ml PRP through a peppering technique (one skin portal and 4–5 penetrations into the fascia). Patients were evaluated at a mean 10 months of follow-up, assessing their level of pain and functional recovery. Significant results were obtained, with almost 90% of patients reporting full satisfaction and complete recovery, being able to get back to their daily activities only 2 weeks after the treatment. Furthermore, US evaluation of plantar fascia thickness before and after the treatment was performed, revealing a significant reduction of this parameter over time. The authors concluded that this regenerative procedure can be considered safe and effective for this kind of pathology.

5. PRP for osteochondral lesions

The conservative application of PRP was tested in a prospective study by Mei-Dan et al. [23] who compared the efficacy of hyaluronic acid (HA) and PRP in 30 patients (15 per group), affected by talar osteochondral lesions not responsive to previous conservative management. The patients were divided into 2 groups: the first one received 3 weekly intra-articular injections of HA (2 ml each); the other one received 3 weekly intra-articular injections of PRP (2 ml each). Patients were evaluated for up to 28 weeks of follow-up. AHFS, AOFAS, and VAS were used to test pain, stiffness and function. PRP was significantly more effective in controlling pain and re-establishing function.

The surgical application of PRP in talar osteochondral lesions has been tested by Giannini and his group in two different studies [24,25]. They described the first clinical application of an innovative arthroscopic one-stage technique involving autologous mesenchymal stem cells (MSCs), PRP and, alternately, porcine collagen powder or HA membrane. The procedure consisted of harvesting bone-marrow-derived cells from the posterior iliac crest of the patients through a traditional marrow needle. Sixty ml of bone marrow-aspirate were collected and immediately put into a cell separator-concentrator to obtain 6-ml of MSCs concentrate. A collagen powder or the HA membrane could then be used. In the former case, 2 ml of MSCs concentrate was added to 1 g of collagen powder and 1 ml of platelet-rich fibrin gel (previously prepared). In the latter case, HA membrane was cut to match the size of the talar ostechondral lesion and then covered with 2 ml of MSCs concentrate and 1 ml of platelet-rich fibrin gel. The entire procedure was performed via ankle arthroscopy and, after the preparation of the lesion site, the biological composite was placed onto the defect through a cannula, using a probe to obtain the best possible fit.

The first clinical trial [24] involved 48 patients (mean age = 28.5 years) affected by focal lesions (mean size = 2.1 cm^2) and evaluated at 6, 12, 18, and 24 months of follow-up using the AOFAS score. A significant increase in this parameter was recorded 6 months after the surgical procedure; this outcome was confirmed up to the final follow-up. The rate of return to high impact sport activity was satisfactory; more than 75% of the patients returned to sport at 11 months of follow-up. These investigators found a correlation between clinical outcome and lesion size; poorer results were found for defects > 3 cm^2, and previous surgery was also shown to negatively affect the outcome. Conversely, the outcome was not influenced by the lesion depth or the type of scaffold used (collagen powder or HA membrane). Five second-look arthroscopies were performed at 1 year of follow-up: in 2 cases biopsies were taken, revealing, after histologic and immuno histologic analysis, the presence of new cartilage tissue with varying degrees of tissue remodeling toward a hyaline aspect. The overall findings suggested that this novel approach could stimulate tissue regeneration with interesting clinical efficacy. According to the authors, results may even be comparable to those of autologous chondrocyte implantation (ACI), but avoiding the double surgical time and the inherent stress for the patient.

Subsequently, the same authors made a further study [25] to compare MSCs + PRP + scaffold with open and arthroscopic ACI. Eighty-one patients were included in this analysis, 10 treated by open ACI, 46 by arthroscopic ACI, and 25 by the MSCs "one-step" technique. The clinical results were compared for up to 3 years of follow-up. AOFAS was the test chosen for clinical evaluation and radiographic analysis was also performed. The clinical improvement in each subgroup was significant and no inter-group difference was observed, thus confirming the possibility of matching the effectiveness of chondrocyte transplantation by a single-step procedure. X-rays showed no sign of progression of osteoarthritis and MRI revealed a good rate of defect filling and integration of the newly regenerated cartilage within the surrounding tissue. Another aspect worth of consideration is the economic one: in fact, the authors pointed out that their novel one-step regenerative technique costs less than an half with respect to the traditional arthroscopic ACI.

6. PRP for syndesmotic fusion in total ankle arthroplasty

PRP has also been used in the field of total ankle replacement (TAR). Barrow and Pomeroy [26] described the application of PRP during TAR procedures to enhance the syndesmotic fusion rate of the tibio-fibular joint: a weak syndesmotic fusion increases the risk of tibial component migration by 8.5 times and, therefore, local application of PRP was tested to achieve a stronger syndesmotic fusion [26]. After debriding the soft tissue in the syndesmosis and drilling the bone surfaces of both tibia and fibula, the authors applied autologous platelet concentrate locally and then to the bone graft used to cover the porous coating of the prosthesis. Final stabilization of the joint was obtained by two cortical screws to compress the fibula carefully against the tibia. Twenty patients were included in this study with a mean follow-up of 15 months. At 6 months' follow-up, 100% of cases had successful fusion and no mobilization of the prosthetic components was reported. The authors compared these results with historical controls from their own experience and found a statistically significant difference in favor of the PRP group (100% vs 62% fusion at 6 months follow-up), thus revealing a new potential application for this blood derivative.

These results were later confirmed by a study performed by Coetzee et al. [27], who compared the results of 66 TARs enhanced by autologous platelet concentrate (the application technique was the same described by Barrow) with 114 implants, without biological adjuvant, previously performed by the same surgeons. Evaluations were performed at 8, 12, and 24 weeks to assess fusion rate in both groups and any delayed and non-unions. The group that received PRP showed superiority in all parameters considered. Fusion at 8 and 12 weeks was significantly higher in the PRP group and a lower occurrence of delayed and non-union was also reported, with a cumulative rate (non-union + delayed unions) of 9% in PRP group vs 27% recorded in the control group.

7. PRP for foot and ankle fusions

A study by Bibbo et al. [28] focused on the use of PRP as a biological enhancer during foot and ankle fusion procedures in patients at high risk of non-union. The following risk factors were considered: smoking, diabetes, medical or pharmacological immunodepression, history of previous non-union, avascular necrosis, current or previous infection at the proposed surgical site, history of open treatment after high energy trauma, multiple previous surgeries at the proposed site and suboptimal arterial supply. Sixty-two patients (mean age: 51 years) were studied, 69% of whom had multiple risk factors. All patients underwent local administration of PRP during the fusion procedure. At 6 months of follow-up, 94% of patients had a successful union with a mean time-to-union of 41 days. Non-union occurred only in 4 cases: two patients developed post-surgical infection before fusion and the other two cases were characterized by multiple previous failed attempts of fusions. The investigators concluded that PRP could be considered a safe and effective method to prevent non-union in high risk patients. Furthermore, the investigators compared their results to those of other research groups who used another approach based on implantable Direct Current Bone Stimulators (DCS): the comparison revealed lower non-union and complication rates in the PRP group.

8. Discussion

The range of applications of PRP is rapidly increasing in orthopedic practice and its use in the foot and ankle district is also destined to rise further in the near future. However, it is important to underline that, at the present moment, it is impossible to define a clear indication for the use of this biological product, neither as a conservative approach nor as a biological enhancer during surgical procedures. In fact, some controversies concerning PRP are still unresolved, although several studies, both pre-clinical and clinical, have been published on a large range of conditions such as knee OA, patellar tendinopathies and rotator cuff repair [29–37]. Concerning this, it should be mentioned that the available literature on this topic mainly consists of reviews rather than clinical trials, thus suggesting that a fervent debate is ongoing about this novel biological treatment [1]. As for any new therapy, and especially those consisting of biological products, the process of establishing clear indications is not easy but, in this particular case, it looks harder than expected.

In vitro studies [38,39] have shown the great potential of platelet-derived GFs to promote the regeneration of several different tissues, including bone, cartilage and tendons, even if some controversial findings have been reported in animal studies [40]. Nevertheless, clinical trials have not been fully able to endorse the encouraging pre-clinical data.

The reasons for this lack of clinical evidence might be both the nature of PRP itself and the quality of the studies published up to the present date.

The first issue concerns the substance itself, and in particular its intrinsic nature. The truth is that even the definition of PRP is not clear and, in general, a large variety of different products are defined by this name: PRP is regarded as a blood derivate generated by differential centrifugation of whole blood, with a higher concentration of platelets compared to basal blood level. More specific elements of PRP have not been uniformly defined. In fact, a commonly accepted platelet concentration is approximately 400% of the peripheral blood PLT count [41,42]. Nonetheless, in the literature, PRP concentrations have been reported to range widely, from 4 to 8 times than those found in whole blood [43], and good results have also been reported with lower concentrations [43,12]. Furthermore, several different procedures have been described to obtain PRP, thus implying the existence of qualitative and quantitative differences among substances used in various pre-clinical and clinical studies.

With regards to preparation procedures [44], it is possible to use either a centrifuge or a cell separator to obtain PRP. Several preparation protocols have been released so that parameters such as the number of centrifugations, acceleration, rotations per minute and duration can vary markedly. The result of this variability is that there are different products characterized by different platelet concentrations, different amounts of GFs and other bioactive molecules, and also different cell types delivered in the final preparation. In fact, some methods, besides increasing the number of platelets, also allow leukocytes and monocytes to be concentrated. The therapeutic role of these cells is controversial: some authors underline their potential anti-bacterial function, whereas others point out that the proteases and reactive oxygen products delivered by leukocytes might have a negative effect [45]. Another relevant aspect is the dose to apply: as for every drug, the therapeutic effect is achieved at a certain range [46], whereas higher doses might be less effective or even detrimental.

Activation is another source of variability: some authors do not activate PRP, whereas others use autologous thrombin, calcium chloride, batroxobin, and even physical methods or biomaterials [44].

Finally, we have to consider the therapeutic protocol itself because, especially for the conservative approach, the number of injections and their timing vary for each research group, thus making comparison among clinical trials very difficult.

In view of all this, the large variability among PRP formulations is one of the greatest obstacles to overcome and then further studies are required to determine which PRP is the best (admitting that it works!) for each specific pathology considered.

Besides exploring the controversial aspects related to the substance itself, it is also fundamental to overview critically the current literature on PRP applications in foot and ankle pathologies. Concerning this, it is easy to notice that the majority of papers currently published do not provide high quality scientific evidence (Table 1).

With regards to the application of PRP in surgical Achilles tendon repair, only two studies have been published: the first one, by Sánchez et al. [12], is a retrospective trial focusing on just 6 patients. The study design, the lack of randomization and the low number of patients included are major weak points so that, even if good results were reported, they could not contribute to a reliable assessment of PRP effectiveness in this particular application. Conversely, the results reported by Schepull et al. [13], whose randomized trial is the "state of the art" in this field, revealed no clinical or biomechanical difference between PRP and control groups; therefore it seems that no indication should be given for the use of PRP in Achilles tendon surgical repair.

Concerning conservative management for tendinopathy, PRP has always been tested as a second-line approach after unsuccessful conservative treatment. A case report and four case series [14,17–20] suggest good results for this approach but they are in contrast with the only randomized double-blind controlled trial [15,16] by deVos et al., who reported no significant difference between PRP and placebo. However, some limitations may also be found in this study: in particular, the mean age of patients was 49.5 years, thus targeting a potentially less responsive population of middle-aged subjects with a low level of sports activity. Furthermore, the investigators performed just a single ultra-sound guided injection of 4 ml non-activated PRP: due to the degenerative nature of the pathology, a single administration of GFs might not be the ideal choice to treat such a chronic condition. The lack of exogenous activation to gelify the platelet concentrate and keep it into the lesion site might have further compromised the clinical outcome, because endogenous

activation of platelets is very slow whereas PRP is rapidly squeezed away from the tendon by muscle contraction, thus reducing the secretion of GFs in the lesion site. In light of these remarks, further studies with high methodological quality need to be performed to show the usefulness or lack of efficacy of PRP.

In the case of plantar fasciitis, the scientific evidence available at the present moment is also not conclusive. The only randomized trial [21] proved no difference in clinical outcome between PRP and corticosteroids at short term evaluation, while the other paper [22] deals with a small cohort of patients without a control group. The only reason to prefer PRP over more traditional corticosteroids seems the fact that PRP apparently does not expose the patient to the potentially dangerous side effects associated with corticosteroids.

The application of PRP to treat osteochondral talar lesions is supported by three studies, one of which deals with an injective approach [23] and two with surgical treatment [24,25]. The randomized trial by Mei-Dan et al. [23] revealed significant results in favor of PRP but the low number of patients and the short-term follow-up evaluation are weak points. Conversely, the studies testing the surgical application of MSCs + PRP + biomaterials (collagen powder or HA membrane) [24,25] are limited because the use of multiple biological autologous and bio-engineered substances makes impossible to determine the real contribution of PRP itself; however, the good clinical outcome is the best premise for further enquiries into that topic in order to confirm the efficacy of this procedure compared to ACI in a long-term evaluation [25].

The use of PRP as a biological enhancer in tibio-talar fusion in total ankle replacement has been explored in two studies [26,27] but neither of them is randomized and comparisons were made only with historical controls. Furthermore, the better clinical outcome might be related, at least partially, to the surgeons' improved surgical skills with experience over time. The results, however, were so significant that a randomized trial would be frankly welcome in an attempt to establish a clinical indication.

The last study examined, authored by Bibbo et al. [28], considers the application of PRP in a large range of procedures (different kinds of fusions in the foot and ankle district) in patients at risk of non-union. The results were interesting but the scarce homogeneity in the surgical treatments analyzed and the lack of randomization is a major concern for establishing whether the application of PRP is really the key factor in determining higher fusion rates.

Although the current evidence for PRP use is poor and a literature analysis shows low-level studies with heterogeneous PRP applications and controversial findings, currently many research groups are performing robust trials that will offer in the near future some answers to the many questions raised by this biological treatment approach.

9. Conclusion

PRP is a fascinating area of pre-clinical and clinical research. At present, concerning foot and ankle applications, there is still no clear clinical indication for its use in any of the particular fields where it has been experimented. Despite the golden aura around its therapeutic potential, further studies are needed both to identify the real biological properties of this product and the best applicative modalities for its use.

Conflict of interest statement

All authors declare no conflict of interest.

Funding sources

No funding sources have been received by the authors for the present study.

References

[1] Filardo G, Kon E. PRP: more words than facts. . .. Knee Surg Sports Traumatol Arthrosc 2012;20(9):1655–6.
[2] Foster TE, Puskas BL, Mandelbaum BR, Gerhardt MB, Rodeo SA. Platelet-rich plasma: from basic science to clinical applications. Am J Sports Med 2009;37(11):2259–72.
[3] Sanchez AR, Sheridan PJ, Kupp LI. Is platelet-rich plasma the perfect enhancement factor? A current review. Int J Oral Maxillofac Implants 2003;18:93–103.
[4] Gobbi A, Bathan L. Biological approaches for cartilage repair. J Knee Surg 2009;22(1):36–44.
[5] Cole BJ, Seroyer ST, Filardo G, Bajaj S, Fortier LA. Platelet-rich plasma: where are we now and where are we going? Sports Health 2010;2(3):203–10.
[6] Boswell SG, Cole BJ, Sundman EA, Karas V, Fortier LA. Platelet-rich plasma: a milieu of bioactive factors. Arthroscopy 2012;28(3):429–39.
[7] 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.
[8] Mishra A, Woodall Jr J, Vieira A. Treatment of tendon and muscle using platelet-rich plasma. Clin Sports Med 2009;28(1):113–25.
[9] Soomekh DJ. Current concepts for the use of platelet-rich plasma in the foot and ankle. Clin Podiatr Med Surg 2011;28(1):155–70.
[10] Gandhi A, Bibbo C, Pinzur M, Lin SS. The role of platelet-rich plasma in foot and ankle surgery. Foot Ankle Clin 2005;10(4):621–37.
[11] Kon E, Filardo G, Di Matteo B, Di Martino A, Marcacci M. Platelet-rich plasma in sports medicine: new treatment for tendon and cartilage lesions. Oper Tech Orthop 2012;22(2):78–85.
[12] Sánchez M, Anitua E, Azofra J, Andía I, Padilla S, Mujika I. Comparison of surgically repaired Achilles tendon tears using platelet-rich fibrin matrices. Am J Sports Med 2007;35(2):245–51.
[13] Schepull T, Kvist J, Norrman H, Trinks M, Berlin G, Aspenberg P. Autologous platelets have no effect on the healing of human achilles tendon ruptures: a randomized single-blind study. Am J Sports Med 2011;39(1):38–47.
[14] Filardo G, Presti ML, Kon E, Marcacci M. Nonoperative biological treatment approach for partial Achilles tendon lesion. Orthopedics 2010;33(2):120–3.
[15] de Vos RJ, Weir A, van Schie HT, Bierma-Zeinstra SM, Verhaar JA, Weinans H, et al. Platelet-rich plasma injection for chronic Achilles tendinopathy: a randomized controlled trial. JAMA 2010;303(2):144–9.
[16] de Jonge S, de Vos RJ, Weir A, van Schie HT, Bierma-Zeinstra SM, Verhaar JA, et al. One-year follow-up of platelet-rich plasma treatment in chronic Achilles tendinopathy: a double-blind randomized placebo-controlled trial. Am J Sports Med 2011;39(8):1623–9.
[17] Gaweda K, Tarczynska M, Krzyzanowski W. Treatment of Achilles tendinopathy with platelet-rich plasma. Int J Sports Med 2010;31(8):577–83.
[18] Finnoff JT, Fowler SP, Lai JK, Santrach PJ, Willis EA, Sayeed YA, et al. Treatment of chronic tendinopathy with ultrasound-guided needle tenotomy and platelet-rich plasma injection. PM R 2011;3(10):900–11.
[19] Owens Jr RF, Ginnetti J, Conti SF, Latona C. Clinical and magnetic resonance imaging outcomes following platelet rich plasma injection for chronic mid-substance Achilles tendinopathy. Foot Ankle Int 2011;32(11):1032–9.
[20] Monto RR. Platelet rich plasma treatment for chronic Achilles tendinosis. Foot Ankle Int 2012;33(5):379–85.
[21] Akşahin E, Doğruyol D, Yüksel HY, Hapa O, Doğan O, Celebi L, et al. The comparison of the effect of corticosteroids and platelet-rich plasma (PRP) for the treatment of plantar fasciitis. Arch Orthop Trauma Surg 2012;132(6):781–5.
[22] Ragab EM, Othman AM. Platelets rich plasma for treatment of chronic plantar fasciitis. Arch Orthop Trauma Surg 2012;132(8):1065–70.
[23] Mei-Dan O, Carmont MR, Laver L, Mann G, Maffulli N, Nyska M. Platelet-rich plasma or hyaluronate in the management of osteochondral lesions of the talus. Am J Sports Med 2012;40(3):534–41.
[24] Giannini S, Buda R, Vannini F, Cavallo M, Grigolo B. One-step bone marrow-derived cell transplantation in talar osteochondral lesions. Clin Orthop Relat Res 2009;467(12):3307–20.
[25] Giannini S, Buda R, Cavallo M, Ruffilli A, Cenacchi A, Cavallo C, et al. Cartilage repair evolution in post-traumatic osteochondral lesions of the talus: from open field autologous chondrocyte to bone-marrow-derived cells transplantation. Injury 2010;41(11):1196–203.
[26] Barrow CR, Pomeroy GC. Enhancement of syndesmotic fusion rates in total ankle arthroplasty with the use of autologous platelet concentrate. Foot Ankle Int 2005;26(6):458–61.
[27] Coetzee JC, Pomeroy GC, Watts JD, Barrow C. The use of autologous concentrated growth factors to promote syndesmosis fusion in the Agility total ankle replacement. A preliminary study. Foot Ankle Int 2005;26(10):840–6.
[28] Bibbo C, Bono CM, Lin SS. Union rates using autologous platelet concentrate alone and with bone graft in high-risk foot and ankle surgery patients. J Surg Orthop Adv 2005;14(1):17–22.
[29] Filardo G, Kon E, Pereira Ruiz MT, Vaccaro F, Guitaldi R, Di Martino A, et al. Platelet-rich plasma intra-articular injections for cartilage degeneration and osteoarthritis: single- versus double-spinning approach. Knee Surg Sports Traumatol Arthrosc 2011 [Epub ahead of print, Dec 28].
[30] Kon E, Mandelbaum B, Buda R, Filardo G, Delcogliano M, Timoncini A, et al. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. Arthroscopy 2011;27(11):1490–501.
[31] Filardo G, Kon E, Buda R, Timoncini A, Di Martino A, Cenacchi A, et al. Platelet-rich plasma intra-articular knee injections for the treatment of degenerative

cartilage lesions and osteoarthritis. Knee Surg Sports Traumatol Arthrosc 2011;19(4):528–35.
[32] Kon E, Buda R, Filardo G, Di Martino A, Timoncini A, Cenacchi A, et al. Platelet-rich plasma: intra-articular knee injections produced favorable results on degenerative cartilage lesions. Knee Surg Sports Traumatol Arthrosc 2010;18(4):472–9.
[33] Filardo G, Kon E, Della Villa S, Vincentelli F, Fornasari PM, Marcacci M. Use of platelet-rich plasma for the treatment of refractory jumper's knee. Int Orthop 2010;34(6):909–15.
[34] Kon E, Filardo G, Delcogliano M, Presti ML, Russo A, Bondi A, et al. Platelet-rich plasma: new clinical application: a pilot study for treatment of jumper's knee. Injury 2009;40(6):598–603.
[35] Spaková T, Rosocha J, Lacko M, Harvanová D, Gharaibeh A. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. Am J Phys Med Rehabil 2012;91(5):411–7.
[36] Randelli P, Arrigoni P, Ragone V, Aliprandi A, Cabitza P. Platelet rich plasma in arthroscopic rotator cuff repair: a prospective RCT study, 2-year follow-up. J Shoulder Elbow Surg 2011;20(4):518–28.
[37] Mishra A, Collado H, Fredericson M. Platelet-rich plasma compared with corticosteroid injection for chronic lateral elbow tendinosis. PM R 2009;1(4):366–70.
[38] Dragoo JL, Braun HJ, Durham JL, Ridley BA, Odegaard JI, Luong R, et al. Comparison of the acute inflammatory response of two commercial platelet-rich plasma systems in healthy rabbit tendons. Am J Sports Med 2012;40(June (6)):1274–81.
[39] Akeda K, An HS, Okuma M, Attawia M, Miyamoto K, Thonar EJ, et al. Platelet-rich plasma stimulates porcine articular chondrocyte proliferation and matrix biosynthesis. Osteoarthritis Cartilage 2006;14:1272–80.
[40] Kon E, Filardo G, Delcogliano M, Fini M, Salamanna F, Giavaresi G, et al. Platelet autologous growth factors decrease the osteochondral regeneration capability of a collagen-hydroxyapatite scaffold in a sheep model. BMC Musculoskelet Disord 2010;11:220.
[41] Marx R. Platelet rich plasma (PRP): what is PRP and what is not PRP. Implant Dent 2001;10:225–8.
[42] Marx RE. Platelet-rich plasma: evidence to support its use. J Oral Maxillofac Surg 2004;62:489–96.
[43] Creaney L, Hamilton B. Growth factor delivery methods in the management of sports injuries: the state of play. Br J Sports Med 2008;42(5):314–20.
[44] Tschon M, Fini M, Giardino R, Filardo G, Dallari D, Torricelli P, et al. Lights and shadows concerning platelet products for musculoskeletal regeneration. Front Biosci (Elite Ed) 2011;3:96–107.
[45] Sundman EA, Cole BJ. Fortier LA Growth factor and catabolic cytokine concentrations are influenced by the cellular composition of platelet-rich plasma. Am J Sports Med 2011;39(10):2135–40.
[46] Torricelli P, Fini M, Filardo G, Tschon M, Pischedda M, Pacorini A, et al. Regenerative medicine for the treatment of musculoskeletal overuse injuries in competition horses. Int Orthop 2011;35(10):1569–76.