

# Platelet-rich plasma in orthopaedic sports medicine: state of the art

Giuseppe Milano,<sup>1</sup> Mikel Sánchez,<sup>2,3</sup> Chris H Jo,<sup>4</sup> Maristella F Saccomanno,<sup>5</sup> Bhavani P Thampatty,<sup>6</sup> James H-C Wang<sup>6</sup>

<sup>1</sup>Department of Orthopaedics, University of Brescia, Brescia, Italy

<sup>2</sup>Advanced Biological Therapy Unit-UTBA, USP La Esperanza Clinic, Vitoria-Gasteiz, Spain

<sup>3</sup>Arthroscopic Surgery Unit, Hospital Vithas San José, Vitoria-Gasteiz, Spain

<sup>4</sup>Department of Orthopedic Surgery, SMG-SNU Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea

<sup>5</sup>Department of Orthopaedics, University Hospital A. Gemelli IRCCS, Rome, Italy

<sup>6</sup>MechanoBiology Laboratory, Department of Orthopaedic Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

## Correspondence to

Prof Giuseppe Milano, Department of Orthopaedics, University of Brescia, Brescia, BS, Italy; giuseppe.milano@outlook.it

Received 31 March 2019

Accepted 9 April 2019

## ABSTRACT

Platelet-rich plasma (PRP) is one of the many new developments within the expanding field of regenerative medicine. It aims to improve the process of tissue repair through local delivery of autologous bioactive agents to influence critical physiological mechanisms such as inflammation, angiogenesis or extracellular matrix synthesis. Within orthopaedics and sports medicine, the use of PRP has been rapidly increasing in popularity as patients seek non-surgical approaches to acute and chronic musculoskeletal injury and disease. The popularity of this new treatment option has prompted a rapid increase in research endeavours. Although preclinical studies were encouraging, clinical studies often reported controversial results. The differences in the composition and application techniques of PRP have made comparisons regarding its efficacy difficult and somehow inconclusive. Although PRP appears to be a safe treatment option with potentially beneficial effects to injured musculoskeletal tissues, continuous efforts are needed to identify factors that influence the biological response to PRP treatment. It is likely that in the near future the PRP preparation will be tailored not only to the specific pathology of interest but also to stage of disease. However, the growing emphasis on an evidence-based approach in the sports medicine setting demands additional research efforts before incorporating this technology in routine clinical care. The current review explores the latest findings on PRP efficacy in several musculoskeletal conditions, focusing on results of the highest level of evidence available.

## INTRODUCTION

Platelet-rich plasma (PRP) represents a biological treatment for various musculoskeletal injuries involving tendons, ligaments, cartilage and bone. It is a refined product of autologous blood with a platelet concentration greater than that of whole blood. It is rich in growth factors (GFs) and cytokines that have been shown to initiate and promote healing by stimulating cell migration, cell proliferation, angiogenesis and matrix synthesis.<sup>1</sup> PRP is actually the most common term used in literature for referring to a cluster of products including autologous conditioned plasma, platelet-enriched plasma, platelet-rich concentrate, autogenous platelet gel, platelet releasate, platelet rich in GFs and others.<sup>2</sup> Differences in PRP include the concentrations of blood cells and bioactive materials. Among them, the concentrations of platelets and leucocytes have been known to play critical roles.<sup>3</sup> Since initial definition, the platelet concentration of PRP of  $10^6$  platelets/ $\mu$ L in a 5 mL volume of plasma has

been used as a 'working PRP',<sup>4</sup> since lesser concentrations cannot be relied on to enhance wound healing, while greater concentrations have not yet been shown to further enhance wound healing.<sup>4</sup> However, optimal platelet concentration is still undetermined. The role of leucocytes in PRP has not been fully elucidated either. Some researchers reported that the presence of leucocytes has some advantages, including anti-infectious and immune regulation potentials.<sup>5-6</sup> In addition, leucocytes can help platelets to promote angiogenesis by the production of vascular endothelial growth factor (VEGF).<sup>7</sup> However, recent in vitro and in vivo evidences demonstrated that the presence of leucocytes in PRP induced predominantly catabolic and inflammatory changes in differentiated tenocytes, whereas leucocyte-poor PRP mainly induced anabolic changes.<sup>8-10</sup> At present, no clinical studies suggest what would be the optimal PRP formulation with respect to the concentration of leucocytes. It could be generally said that, so far, same PRP has been applied to different conditions without consideration of kind and stage of injuries and diseases.

PRP is usually prepared with a commercial kit, which instructed to apply a predetermined dose for all types of injuries and diseases including osteoarthritis (OA), rotator cuff (RC) disease, Achilles tendinopathy, epicondylitis and so on. Furthermore, no consensus has been reached about the choice of PRP for certain stage of injuries and disease. Yuan *et al* suggested leucocyte-rich PRP for acute soft tissue injuries.<sup>11</sup> Zhou *et al* suggested that leucocyte-rich PRP could benefit early-phase healing because of its ability to fight off infections, whereas leucocyte-poor or pure PRP could be used for late-stage healing because of its anabolic effects. It can also be said that 'one-size-fits-all' approach would not bring about optimal results and individualisation should be necessary.<sup>8</sup> Further studies are requested for determining optimal time and choice of PRP.

Definitely, the theoretical concept that concentrating platelets at the injured site could accelerate and optimise the healing mechanisms set the rationale for the development of a myriad of studies to investigate the therapeutic applications of PRP for various orthopaedic injuries. Although the in vitro effects have been promising, only a few randomised clinical trials (RCTs) have demonstrated favourable clinical translation.<sup>1-2</sup> Contrasting clinical results may be due to the heterogeneity of PRP formulations. However, the increase in recently published studies has prompted the present narrative review



© International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine 2019. No commercial re-use. See rights and permissions. Published by BMJ.

**To cite:** Milano G, Sánchez M, Jo CH, *et al*. *JISAKOS* Epub ahead of print: [please include Day Month Year]. doi:10.1136/jisakos-2019-000274

of the literature, exploring the current indications for clinical use of PRP, emphasising its effectiveness and safety.

### PRP in cartilage defects and knee OA

The treatment of cartilage injuries remains daunting despite both advances in pharmacological management of pain and inflammation and advances in the surgical procedures and techniques. Concerning cartilage defects, current treatments aim to achieve the restoration of hyaline cartilage, and although there is a wide range of surgical options such as microfracture, osteochondral autograft or allograft transfer, or autologous chondrocyte implantation, the perfect hyaline cartilage has not yet been achieved. To overcome this drawback, new treatments based on regenerative medicine are emerging, namely PRP, mesenchymal stem cells (MSCs) or gene therapy.<sup>12</sup> Focusing on the PRP, the use of this therapy as an adjuvant in surgical techniques for chondral defects involves new perspectives in surgery based on synergetic effects of PRP on cartilage repair. Particularly, it presents a chondroprotective<sup>13 14</sup> and an anti-inflammatory effect on human chondrocytes.<sup>15 16</sup>

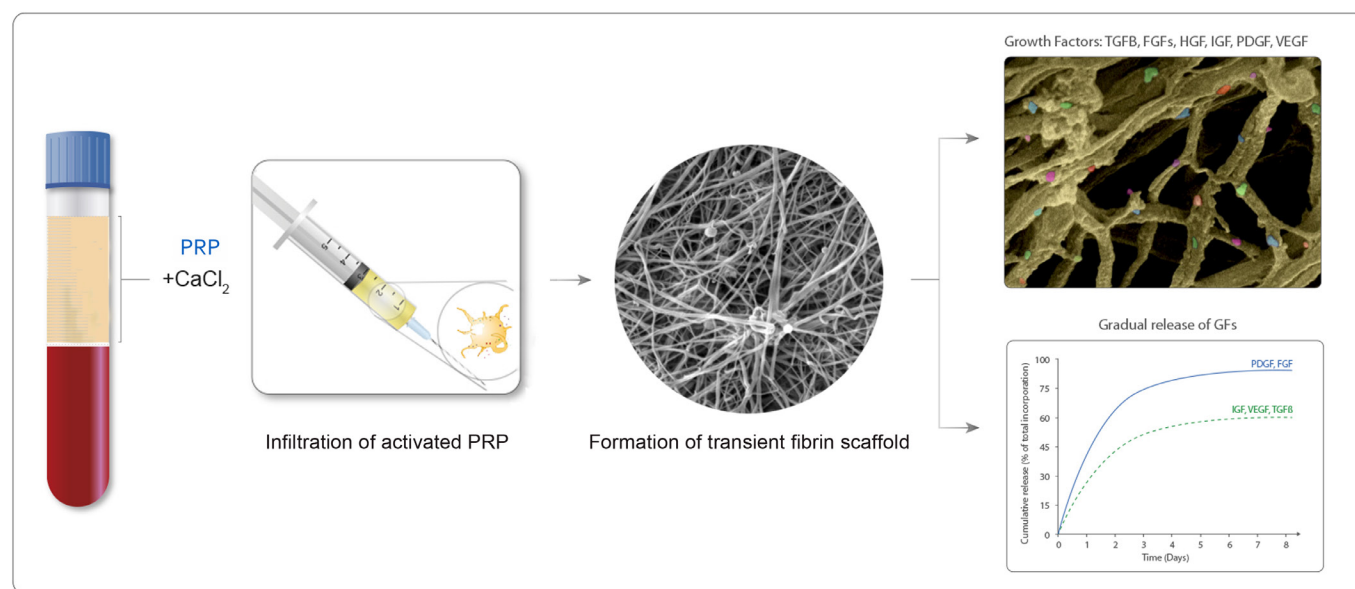
Similarly, among the new emerging therapies to address knee OA, PRP is one of the most outstanding treatments. Indeed, intra-articular infiltrations of PRP transports many bioactive mediators within an autologous fibrin network, which are released gradually and several groups have proven to considerably reduce pain, improve joint stiffness and physical function in patients with knee OA.<sup>17-19</sup>

Platelet GFs and fibrin, together with plasmatic GFs (hepatocyte growth factor (HGF) and insulin-like growth factor-1 (IGF-1)) present within PRP, stimulate cell proliferation and migration, synthesis and deposition of extracellular matrix (ECM) components, angiogenesis and tissue remodelling.<sup>20</sup> Thus, the injection of PRP in its liquid formulation delivers GFs locally, and simultaneously mimics and amplifies the spontaneous healing response in injured areas and in special cell niches, which would otherwise be inaccessible. This in situ generated fibrin bioscaffold interacts with ECM proteins and cells, binding to fibronectin,<sup>21</sup> achieving

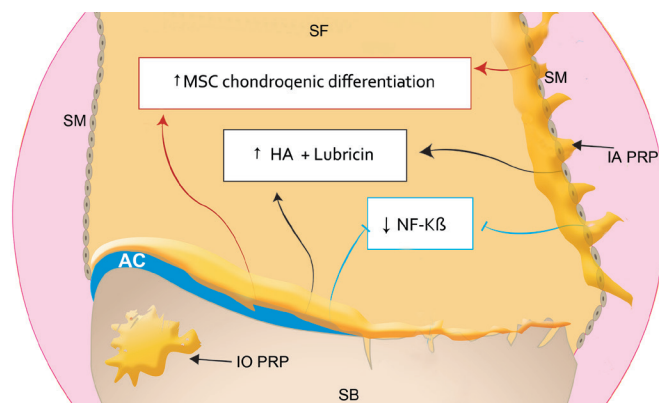
a transient three-dimensional scaffold which will gradually release GFs and maintain their concentration at the site of the scaffold formation (figure 1).

Cartilage loss is not considered the key pathological process that causes knee OA. The initiating factor seems to be the result of a malfunction present in the whole joint, including all tissues crucial for maintaining articular homeostasis.<sup>22</sup> Considering this aspect, and with the aim of repairing a physiological homeostatic network at the tissue level in synovial joint failure, new therapeutic approaches are needed. Currently, intra-articular delivery is the conventional modality to deliver PRP in patients who suffer from knee OA and it has been shown to be safe and efficacious in improving clinical symptoms. However, this route does not target subchondral bone, and some mechanistic and dosage aspects remain to be elucidated in order to determine, harness, and optimise the therapeutic potential of PRP products.<sup>23</sup> Since the subchondral bone has been proposed as a target, intraosseous infiltrations are gaining attention to achieve better results in several osteochondral damages. PRP administered in an intraosseous way acts directly in the subchondral bone, whose role in the pathophysiology of knee OA is increasingly recognised.<sup>24 25</sup> Lesions on the subchondral bone lead to a pathological condition, and elevated crosstalk between the subchondral bone and the cartilage appears, disrupting homeostasis and facilitating an inflammatory environment in the joint. The action of PRP on this structure could restore homeostatic balance, reduce the presence of inflammatory mediators, and modulate the aberrant fibrovascular tissue typical of joint pathologies. After the intraosseous injection, GFs gain access to the subchondral bone and deep layers of cartilage because of mechanical and biological connections between these two tissues, thus achieving an upregulation of transforming growth factor- $\beta$  and PRP (figure 2).

The association with MSCs is an alternative method of obtaining the positive effect of PRP on cartilage pathologies, since PRP may directly enhance the reparative properties of the MSCs administrated into the knee or seeded at the cartilage defect.<sup>26</sup> Indeed, MSCs hold an important therapeutic potential



**Figure 1** After platelet-rich plasma (PRP) preparation and activation, it is infiltrated as a liquid formulation that will become a transient scaffold. The generated fibrin matrix is embedded with a pool of growth factors stemmed from activated platelets and plasma. They are released in a gradual and sustained manner at the dysfunctional and degenerated sites as the fibrinolytic occurs. GFs, growth factors; PDGF, platelet-derived growth factor; TGF- $\beta$ , transforming growth factor- $\beta$ ; VEGF, vascular endothelial growth factor.



**Figure 2** Intra-articular (IA) and intraosseous (IO) infiltrations of platelet-rich plasma (PRP) stimulate the synthesis of hyaluronic acid (HA) and lubricin by synoviocytes and chondrocyte, favour a homing and chondrogenic differentiation effect on mesenchymal stem cells (MSCs) of subchondral bone (SB) and synovial fluid (SF), and suppress NF- $\kappa$ B pathway activation. As a result, concentration cytokines is reduced, inflammation is dampened and SF homeostasis is restored. AC, articular cartilage; NF- $\kappa$ B, nuclear factor kappa B; SM, synovial membrane.

promoting regeneration, derived from their proliferative and multipotential differentiation properties, along with their anti-apoptotic effect. These cells could lead to the formation of new chondrocytes and cartilage regeneration, a process that has been observed in promising preclinical studies and clinical trials.<sup>27–29</sup>

It should be taken into account that current treatments only relieve symptoms and do not stop the course of the disease, and this often forces the patient to repeat the previously mentioned treatments or to undergo a total joint replacement. Treatments that stop or slow knee OA are necessary to prevent or delay surgery, improve the quality of life and avoid the economic costs of this condition.

### PRP in tendon injuries

Tendon injuries and rupture have become a widespread problem not only in young athletes but also in general population, particularly in ageing population. The most common affected tendons include those around elbow and wrist and those of patellar and Achilles tendinopathies, and RC.

#### Lateral epicondylitis

Lateral epicondylitis (LE) has a reported prevalence of 3%. Conservative therapies include rest, physical therapy and/or steroid injections. Recently, PRP has garnered greater attention as a potential long-term treatment option in severe cases. Mishra and Pavelko<sup>30</sup> were the first to report the use of PRP for patients considering surgery for chronic severe elbow tendinosis. The authors found 60% improvement in pain scores for PRP-treated patients versus a 16% improvement in control patients 8 weeks after treatment. Moreover, at final follow-up (mean, 25.6 months; range, 12–38 months), the PRP patients reported over 90% reduction in pain compared with pretreatment scores. Subsequently, several studies have been published on this topic and recent meta-analysis have been conducted.<sup>31–32</sup> Arirachakaran *et al*<sup>31</sup> published a network meta-analysis including 10 RCTs, of which 7 compared PRP with either autologous blood or steroids. The authors found that PRP led to a significant reduction in Visual Analogue Scale (VAS) pain scores compared with steroids. However, when PRP was compared with autologous blood, no significant differences were observed. Functional

outcomes, as measured by the Disabilities of the Arm, Shoulder and Hand (DASH) score, also displayed a significant benefit in favour of PRP in comparison to both steroids and autologous blood at 3-month follow-up.

#### Patellar tendinopathy

Patellar tendinopathy or jumper's knee is a common overuse tendon disorder.

PRP may offer opportunities in aiding regeneration of tissue with low healing potential. High-quality evidence on PRP efficacy on this topic is still limited. However, a recent meta-analysis including only two RCT studies, comparing PRP injections with extracorporeal shockwave therapy and dry needling of the tendon, showed no significant difference at 3 months, but superior results in favour of PRP treatment at longer follow-up (6 months or longer).<sup>33</sup>

#### Achilles tendinopathy/rupture

Achilles tendinopathy is one of the most frequent ankle and foot overuse injuries.<sup>34</sup>

Besides standard conservative treatment modalities, the administration of PRP injections have also been proposed. A recent systematic reviews found only 3 RCTs and 17 non-randomised trials.<sup>35</sup> Although non-randomised trials showed encouraging results with good return to sport participation and beneficial effects lasting up to midterm, RCTs failed to show any superiority of PRP compared with placebo or physiotherapy.

In case of Achilles tendon ruptures, surgical treatment is required. No beneficial effect of PRP administration during and/or immediately after tendon suturing has been documented.<sup>35</sup> In particular, the only RCT available<sup>36</sup> revealed that PRP addition could be even detrimental in tissue healing since no biomechanical advantages and lower performance were reported in PRP patients with respect to the 'suture-alone' group.

#### PRP in RC tears

RC repair has shown high satisfactory results in patients with RC tear. However, despite advances in biomechanical strategies for enhancing the structural integrity after repair, retear rate is still high, especially in large to massive tears, due to inferior quality of healing caused by failure of regeneration of native tendon to bone interface.<sup>37</sup> Thus, two main questions about the use of PRP in RC repair would be its effect on the quality and speed of healing after repair.

In contrast to promising results in basic research literature, most clinical studies using PRP in RC repair have failed to demonstrate superior outcomes to conventional repair. To our knowledge, more than 40 original clinical studies with respect to effects of PRP on RC disease were reported in English language publications. A large portion of these studies is RCTs or, at least, comparative studies with controls (table 1).

A recent systematic review of RCTs comparing PRP or platelet-rich fibrin with a control group in arthroscopic RC repair showed that the use of PRP results in improved healing rates, pain levels and functional outcomes especially in large tears (>3 cm).<sup>38</sup> Previously, Warth *et al* reported significantly lower retear rates with PRP application in patients who underwent double-row repair for large RC tears in subgroup analysis of a meta-analysis of 11 level 1 or 2 studies.<sup>39</sup> In contrast, Vavken *et al*<sup>40</sup> and Chahal *et al*<sup>41</sup> reported that PRP would be effective in reducing retear rates in small and medium RC tears. Although these studies seemed to report divergent conclusions, they all suggest that PRP may have a potential role in enhancing RC

# State of the Art

**Table 1** Clinical studies of PRP for RC tear

No	Year	Author	Stage of disease	Usage	Design	Clinical outcomes	Structural outcomes
1	2008	Everts	Impingement	Surgery	RCT	Better	NA
2		Randelli	RC tear	Surgery	Case series	Improved	NA
3	2011	Castrocinini	RC tear	Surgery	RCT	No difference	No difference
4		Jo	RC tear	Surgery	Case series	No difference	No difference
5		Randelli	RC tear	Surgery	RCT	No difference except for <1 month	No difference
6		Barber	RC tear	Surgery	RCT	No difference except for Rowe	Better
7		Marquez	RC tear	Surgery	RCT	No difference	No difference
8	2012	Gumina	RC tear	Surgery	RCT	No difference	Better
9		Bergeson	RC tear	Surgery	RCT	No difference	Worse
10		Rodeo	RC tear	Surgery	RCT	No difference	No difference
11		Malavolta	RC tear	Surgery	Case series	Improved	No difference
12	2013	Ruiz-Moneo	RC tear	Surgery	RCT	No difference	No difference
13		Scarpone	RC tear	Injection	Case series	Improved	Improved
14		Weber	RC tear	Surgery	RCT	No difference	No difference
15		Antuna	RC tear	Surgery	RCT	No difference	No difference
16		Jo	RC tear	Surgery	RCT	No difference	Better
17		Rha	RC tear	Injection	RCT	Better	NA
18		Kesikburun	RC tear	Injection	RCT	No difference	NA
19	2014	Charousset	RC tear	Surgery	RCT	No difference	No difference
20		Zumstein	RC tear	Surgery	RCT	No difference	No difference
21		Malavolta	RC tear	Surgery	RCT	No difference	No difference
22		Wertherl	RC tear	Surgery	Case-control	No difference	No difference
23	2015	Hak	RC tear	Surgery	RCT	No difference	NA
24		Wang	RC tear	Surgery	RCT	No difference	No difference
25		Von Wehren	RC tear	Injection	Case-control	Better in early	No difference
26		Jo	RC tear	Surgery	RCT	No difference	Better
27		Ilhanli	RC tear	Injection	RCT	No difference except for DASH	NA
28		Carr	Tendinopathy	Surgery	RCT	No difference	NA
29	2016	Zhang	RC tear	Surgery	RCT	No difference	Better
30		Wesner	RC tear	Injection	Case series	Better	Better
31		Say	RC tear	Injection	Case-control	Worse	NA
32		Shams	RC tear	Injection	RCT	Better at 12 weeks	No difference
33		Pandey	RC tear	Surgery	RCT	Better	Better in large only
34		Holtby	RC tear	Surgery	RCT	Better at 1 month in pain reduction	No difference
35		Flury	RC tear	Surgery	RCT	No difference	No difference
36		Barber	RC tear	Surgery	RCT	No difference	No difference
37		Zumstein	RC tear	Surgery	RCT	No difference	No difference
38		D'Ambrosi	RC tear	Surgery	RCT	Better at 1 month in pain reduction	No difference
39		Gwinner	RC tear	Surgery	RCT	No difference	No difference
40	2017	Sengodan	RC tear	Injection	Case series	Improved	Improved
41		Ladermann	RC tear	Injection	Case series	Improved	Improved
42		Kim	RC tear	Injection	Case series	Better	No difference
43		Ebert	RC tear	Surgery	RCT	No difference except for abduction power	No difference

DASH, Disabilities of the Arm, Shoulder and Hand score; NA, not available; PRP, platelet-rich plasma; RC, rotator cuff; RCT, randomised controlled trial.

healing after repair. We believe that controversies regarding effects of PRP in RC repair are raised from differences in 4Ds: Drug (PRP); Delivery (application method); Disease (stage of disease) and Donor (patients). For further elucidation of effects and mechanism of PRP in RC tear, larger well-organised controlled trial would be necessary, but only with careful consideration of the 4Ds. Moreover, efforts to standardise the process and to provide adequate information that could characterise PRP should be attempted for defining the optimal PRP formulation to manage RC injuries. It has been applied through either in liquid form or in solid form of gel. Injection of PRP in liquid form would be simple and easy. However, when used

in arthroscopic RC repair, concerns have been raised regarding risks of dissipation of injected PRP due to the arthroscopic environment. Application of PRP gels may avoid this problem. However, threading and passing gels through the cannula could be more technically demanding. Furthermore, as gelation is usually done by adding calcium with or without thrombin, this could not completely avoid the risk of bioactive materials loss especially which are immediately released with gelation. Lastly, while most studies reported results with autologous PRP, there may be certain conditions in which autologous PRP is not available or appropriate such as patients with haematological diseases, elderly patients with multiple comorbidities, patients who do not



want to draw blood for any reason, and so on. Autologous PRP might not be optimal for patients with diabetes mellitus since it has been reported that expression of platelet-derived growth factor decreased in diabetic animals,<sup>42</sup> and for patients who take antiplatelet medication such as aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) as these drugs significantly impaired platelet function which may result in reduced therapeutic effects of PRP.<sup>43</sup> Under these circumstances, allogeneic PRP could be an option. Jo *et al* recently reported that allogeneic PRP in arthroscopic RC repair did not cause any local or general complications and that it has the efficacy comparable to autologous PRP with respect to the clinical and structural outcomes.<sup>44</sup>

For now, certainly we do not find solid clinical evidences supporting the use of PRP for treatment of RC tears, thus PRP may not be yet recommended for routine use in clinical practice. However, this does not necessarily mean that we should abandon PRP or stop studying. On the contrary, now is the time for conducting better clinical studies with careful consideration of 4Ds of PRP to answer the simple question from patients, 'Is PRP good for RC tear?'

## Other indications

### Ulnar collateral ligament injury

Tears of the ulnar collateral ligament (UCL) are common in overhead-throwing athletes.<sup>45</sup> Surgery is usually reserved to patients with complete tears of the ligament or partial tears who have failed non-operative treatment. Standard non-operative treatments consist of activity modification, use of NSAIDs and a structured physical therapy programme. However, the use of PRP has been also explored.<sup>46–48</sup> Podesta *et al*<sup>46</sup> showed that a single leucocyte-rich PRP injection was a safe adjunct to standard non-operative management in partial UCL tears of 34 overhead-throwing athletes, with 88% of patients returning to their prior level of competition after an average rehabilitation course of 20 weeks. Subsequently, Deal *et al*<sup>47</sup> showed that 22 out of 23 (96%) overhead athletes were able to return to play and demonstrated reconstitution of the medial UCL on MRI after two injections of leucocyte-rich PRP. Moreover, Hoffman *et al*<sup>48</sup> examined the feasibility of using a dermal allograft, PRP and MSCs construct to augment the UCL reconstruction in a professional baseball pitcher.

### Anterior cruciate ligament reconstruction

Anterior cruciate ligament (ACL) tears are among the most common sports-related injuries. Up to now, there is an increasing demand for minimally invasive options to enhance intrinsic ACL healing especially in case of partial ruptures. Managing of partial tears can be very challenging, ranging from non-operative treatment to surgery (augmentation or traditional reconstruction). Unlike other ligaments, the ACL possesses limited intrinsic capacity for spontaneous healing after injury, due to its intra-articular location and a thin synovial membrane.<sup>49</sup> The use of biological approaches, including different GFs, PRP, MSCs, biological scaffolds and augmented ACL primary repair, has been the focus of current research in ACL-accelerated repair and healing. Several in vitro and animal studies demonstrated that intraligamentary administration of PRP determines an increase in cellular density and neovascularisation of the ACL. This results in a better organisation of collagen fibres for superior tensile resistance and biomechanical properties.<sup>50</sup> In light of these findings, the application of PRP augmentation in clinical practice appeared justified. Regarding treatment of partial tears, only two clinical studies evaluated the effect of intraligamentary

injections of PRP, reporting satisfactory clinical results<sup>51 52</sup> and signs of ACL healing at MRI evaluation performed at average 3 months from the procedure.<sup>52</sup> On the opposite, recent systematic reviews focused on the effect of PRP in ACL reconstruction and highlighted some controversies. It has been shown that intraoperative use of PRP is safe because no complications or adverse reaction were reported, and it maybe play a positive role in the healing mechanisms after ACL surgery for what regards graft maturation over time. However, no beneficial effects in terms of clinical outcome, bone-graft integration and prevention of bony tunnel enlargement have been proved.<sup>50 53</sup>

### Patellar tendon donor site in ACL reconstruction

The bone-patellar tendon-bone ligament is a widely used autograft for ACL reconstruction. Donor site complications include anterior knee pain, ranging from 4% to 60%.<sup>54</sup> The empty space or gap left in place after graft harvest has been defined as the cause of persistent discomfort and pain at the donor site for several months, even at rest.<sup>55</sup> Recent studies showed that the application of PRP to the harvest site contributed to accelerated and better healing response evaluated by MRI and provides significant earlier improvement of pain scores in the first 2 months measured by VAS.<sup>55 56</sup> Therefore, based on these findings, PRP could be at least considered as a valid option to address the problem of donor-site morbidity when the patellar tendon is the surgeon's choice for graft harvesting.

### Meniscal tears

Meniscal lesions in the avascular zone are still an unsolved problem in sports traumatology, and most of the time partial meniscectomy is the only treatment option. Unfortunately, the loss of meniscus predisposes the knee joint to degenerative changes.<sup>57</sup> Several in vitro or animal studies have demonstrated that injection of GFs or PRP could increase meniscal cell activity and stimulate repair.<sup>58 59</sup> However, few clinical studies are available: three case-control studies<sup>60–62</sup> and one case report<sup>63</sup> showing controversial results. Some authors reported encouraging results when a single or multiple percutaneous PRP injections are administered weekly<sup>61 63</sup> or when a single injection is performed right after an open meniscal repair.<sup>62</sup> PRP seemed to be effective in relieving pain and stopping tear progression on MRI. Conversely, Griffin *et al*<sup>60</sup> showed no differences in terms of functional results and reoperation rate after arthroscopic meniscal repair with or without a single PRP injection. However, given the lack of power and nature of those studies, no definitive conclusions can be drawn.

### Plantar fasciitis

Plantar fasciitis (PF) is a common foot complaint that affects both active people and physically inactive middle age group. Conservative treatments have always been the first approach for treating PF with great success. However, around 10% of patients seemed not to respond positively.<sup>64</sup> Therefore, PRP injections into the plantar fascia, with or without ultrasound guidance, have been recently introduced as an alternative therapy. Recent systematic reviews, comparing corticosteroid versus PRP injections, reported controversial results. Three reviews without meta-analysis reported superiority of PRP treatment.<sup>64–66</sup> On the opposite, two recent meta-analysis of nine RCTs failed to confirm those data.<sup>67 68</sup> Tsikopoulos *et al*<sup>67</sup> showed that corticosteroid injections are more effective in pain relief in the short term, whereas Yang *et al*<sup>68</sup> reported no differences in short and

## Box 1 Key articles

1. Marx RE (2001) Platelet-rich plasma (PRP): what is PRP and what is not PRP? *Implant Dent* 10:225–228.
2. Mishra A, Pavelko T (2006) Treatment of chronic elbow tendinosis with buffered platelet-rich plasma. *Am J Sports Med* 34:1774–1778.
3. Zimmermann R, Arnold D, Strasser E, *et al* (2003) Sample preparation technique and white cell content influence the detectable levels of growth factors in platelet concentrates. *Vox Sang* 85:283–289.
4. Dohan DM, Choukroun J, Diss A, *et al* (2006) Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part III: leucocyte activation: a new feature for platelet concentrates? *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 101:e51–e55.
5. Zhang JY, Fabricant PD, Ishmael CR, *et al* (2016) Utilization of platelet-rich plasma for musculoskeletal injuries: an analysis of current treatment trends in the United States. *Orthop J Sports Med* 4:2325967116676241.
6. Campbell KA, Saltzman BM, Mascarenhas R, *et al* (2015) Does intra-articular platelet-rich plasma injection provide clinically superior outcomes compared with other therapies in the treatment of knee osteoarthritis? A systematic review of overlapping meta-analyses. *Arthroscopy* 31:2213–2221.
7. Arirachakaran A, Sukthuyat A, Sisayanarane T, *et al* (2016) Platelet-rich plasma versus autologous blood versus steroid injection in lateral epicondylitis: systematic review and network meta-analysis. *J Orthop Traumatol* 17:101–112.
8. Chahal J, Van Thiel GS, Mall N, *et al* (2012) The role of platelet-rich plasma in arthroscopic rotator cuff repair: a systematic review with quantitative synthesis. *Arthroscopy* 28:1718–1727.
9. Andia I, Sánchez M, Maffulli N (2011) Platelet rich plasma therapies for sports muscle injuries: any evidence behind clinical practice? *Expert Opin Biol Ther* 11:509–518.
10. Andriolo L, Di Matteo B, Kon E, *et al* (2015) PRP augmentation for ACL reconstruction. *BioMed Res Int* 2015:371746.

intermediate effects and only limited evidence supporting PRP superiority for long-term pain relief.

## Muscle injuries

Muscle injuries represent up to 55% of all sports injuries and are a challenging problem in sports traumatology.<sup>69</sup> Available treatment options range from rest, ice, compression and

## Box 2 Key issues of patient selection

- Platelet-rich plasma (PRP) might provide some benefit in patients who have knee osteoarthritis, lateral epicondylitis and ulnar collateral ligament injury.
- Inconsistent or minimal benefits are reported for PRP usage in rotator cuff repair, patellar and Achilles tendinopathies, anterior cruciate ligament (ACL) repair/reconstruction, donor site of patellar tendon in ACL reconstruction, meniscal repair, muscle injuries and plantar fasciitis.
- No clinical studies suggest what would be the optimal PRP formulation with respect to the concentration of leucocytes.
- Up to now, PRP has been applied to different conditions without consideration of kind and stage of injuries and diseases.

## Box 3 Essential and/or typical features of platelet-rich plasma (PRP)

- Most common term referred to a cluster of products including: autologous conditioned plasma, platelet-enriched plasma, platelet-rich concentrate, autogenous platelet gel, platelet releasate, platelet rich in growth factors and others.
- Refined product of autologous blood with a platelet concentration greater than that of whole blood.
- Platelet concentration of  $10^6$  platelets/ $\mu$ L in a 5-mL volume of plasma is defined as 'working PRP'.
- Differences in PRP preparations include the concentrations of platelets, leucocytes and bioactive materials.
- Main advantages: autologous biological product, accessible, easily prepared, minimal complications, wide range of potential therapeutic actions.

elevation to anti-inflammatory medications, rehabilitation exercise programmes, electrotherapeutic modalities, hyperbaric oxygen therapy and prolotherapy injections.<sup>70</sup> Clinical evidence to support the use of these modalities is limited and they are generally not sufficient to enhance muscle regeneration efficiently especially when fast resumption of sport activity is a primary target. Recently, several clinical studies on professional athletes investigated the role of PRP.<sup>71 72</sup> PRP therapies may influence muscle regeneration by acting on the myogenic precursors,<sup>73</sup> which are located between the basal lamina and the plasma membrane of each individual myofibre and are quiescent in the uninjured state. Their activities are controlled by GFs and other cytokines, including IGFs, HGF, VEGF, basic FGF or angiopoietin type 1, plasmin and urokinase plasminogen. Once activated, however, they proliferate and differentiate into multinucleated myotubes and, eventually, myofibres.<sup>74</sup>

In clinical management of muscle injuries, the current hypothesis is that intramuscular injections of PRPs deliver supraphysiological concentrations of the above-mentioned factors at the injured site, influencing cell migration, proliferation, differentiation or fusion and ultimately enhancing muscle regeneration.<sup>71</sup>

Few randomised studies are available.<sup>75–78</sup> Indeed, most of the non-randomised studies affirmed that PRP improves quality of repair tissue<sup>79</sup> or accelerates the functional recovery by enhancing several aspects of myogenesis and, therefore, allowing an earlier resumption of sports activities.<sup>72 80 81</sup> However, RCT showed controversial results.<sup>75–78</sup> A Hamid *et al*<sup>77</sup> showed that a single autologous PRP injection combined with a rehabilitation programme was significantly more effective in functional recovery, time to return to sport and pain management than a rehabilitation programme alone in a group of 28 patients affected by hamstring injuries. On the opposite, subsequent studies showed no benefit of intramuscular PRP administration compared with placebo injections in athletes with acute hamstring injuries in the time to healing; time to return to

## Box 4 Major pitfalls of platelet-rich plasma (PRP)

- Optimal concentration of platelets and leucocytes has not been defined.
- Contrasting clinical results may be due to the heterogeneity of PRP formulations.
- No consensus has been reached about the choice of PRP for certain stage of injuries and disease.

play; reinjury rate and alterations of subjective, clinical or MRI measures.<sup>75 76 78 82</sup>

## Future perspectives

PRP has numerous advantages as an autologous biological product for the treatment of musculoskeletal injuries: it is accessible, easily prepared, has minimal complications, and has a broad range of potential therapeutic actions. Moreover, its safety allows basic science and clinical research to be interdependent rather than successive steps. However, some concerns arise about conflicting clinical results for different pathological conditions and about the paucity of guidelines developed by professional organisations. The present review showed that PRP might provide some benefit in patients who have knee OA, LE and UCL injury. On the other hand, current evidence is inconsistent or displays minimal benefits for PRP usage in RC repair, patellar and Achilles tendinopathies, ACL repair/reconstruction, donor site of patellar tendon in ACL reconstruction, meniscal repair, muscle injuries and PF. That being said, it must be highlighted that available systematic reviews and meta-analyses have limited statistical pooling and subgroup analyses. Future meta-analyses should focus on performing subgroup analysis based on the type of PRP preparation used to determine whether the effects differ based on the different formulations. Currently, there is insufficient literature to support a consensus on the optimal PRP preparation for each indication, dose volume, dosing interval, and whether activation is necessary, and if so, by what method. Probably not only different pathologies but also different stages of a disease will require different types of PRP. Therefore, further research into this field is justified by the idea that regenerative medicine would like to move from an old concept 'one-size-fits-all' to a 'patient-tailored' therapy. Rigorous cost-effective analysis, defined algorithms and evidence-based protocols are needed before drawing definitive conclusion on PRP efficacy. So far, the clinician who supports the use of PRP should consider the biology of the condition being treated and the intended goal for PRP therapy. In the same way, patients should be informed that while PRP has several theoretical advantages with minimal complications, its use is still investigational.

**Contributors** GM conceived the idea behind the manuscript, supervised the work and corrected the various draft. MS, CHJ, MFS, BPT and JH-CW performed the literature searches, analysed the data and wrote the first draft. All the authors read and approved the final draft of this manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Provenance and peer review** Commissioned; externally peer reviewed.

## REFERENCES

- Zhang JY, Fabricant PD, Ishmael CR, et al. Utilization of Platelet-Rich Plasma for Musculoskeletal Injuries: An Analysis of Current Treatment Trends in the United States. *Orthop J Sports Med* 2016;4:2325967116676241.
- Willits K, Kaniki N, Bryant D. The use of platelet-rich plasma in orthopedic injuries. *Sports Med Arthrosc Rev* 2013;21:225–30.
- Zimmermann R, Arnold D, Strasser E, et al. Sample preparation technique and white cell content influence the detectable levels of growth factors in platelet concentrates. *Vox Sang* 2003;85:283–9.
- Marx RE. Platelet-rich plasma (PRP): what is PRP and what is not PRP? *Implant Dent* 2001;10:225–8.
- Moojen DJ, Saris DB, Auw Yang KG, et al. The correlation and reproducibility of histological scoring systems in cartilage repair. *Tissue Eng* 2002;8:627–34.
- Dohan DM, Choukroun J, Diss A, et al. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part III: leucocyte activation: a new feature for platelet concentrates? *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006;101:e51–e55.
- Werther K, Christensen IJ, Nielsen HJ. Determination of vascular endothelial growth factor (VEGF) in circulating blood: significance of VEGF in various leucocytes and platelets. *Scand J Clin Lab Invest* 2002;62:343–50.
- Zhou Y, Zhang J, Wu H, et al. The differential effects of leukocyte-containing and pure platelet-rich plasma (PRP) on tendon stem/progenitor cells - implications of PRP application for the clinical treatment of tendon injuries. *Stem Cell Res Ther* 2015;6:173.
- Pifer MA, Maerz T, Baker KC, et al. Matrix metalloproteinase content and activity in low-platelet, low-leukocyte and high-platelet, high-leukocyte platelet rich plasma (PRP) and the biologic response to PRP by human ligament fibroblasts. *Am J Sports Med* 2014;42:1211–8.
- Zhang L, Chen S, Chang P, et al. Harmful Effects of Leukocyte-Rich Platelet-Rich Plasma on Rabbit Tendon Stem Cells In Vitro. *Am J Sports Med* 2016;44:1941–51.
- Yuan T, Guo SC, Han P, et al. Applications of leukocyte- and platelet-rich plasma (L-PRP) in trauma surgery. *Curr Pharm Biotechnol* 2012;13:1173–84.
- Richter DL, Schenck RC, Wascher DC, et al. Knee Articular Cartilage Repair and Restoration Techniques: A Review of the Literature. *Sports Health* 2016;8:153–60.
- Cheng M, Johnson VM, Murray MM. Effects of age and platelet-rich plasma on ACL cell viability and collagen gene expression. *J Orthop Res* 2012;30:79–85.
- Sakata R, Reddi AH. Platelet-Rich Plasma Modulates Actions on Articular Cartilage Lubrication and Regeneration. *Tissue Eng Part B Rev* 2016;22:408–19.
- van Buul GM, Koevoet WL, Kops N, et al. Platelet-rich plasma releasate inhibits inflammatory processes in osteoarthritic chondrocytes. *Am J Sports Med* 2011;39:2362–70.
- Leong DJ, Li YH, Gu XJ, et al. Physiological loading of joints prevents cartilage degradation through CITED2. *Faseb J* 2011;25:182–91.
- Sánchez M, Fiz N, Azofra J, et al. A randomized clinical trial evaluating plasma rich in growth factors (PRGF-Endoret) versus hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis. *Arthroscopy* 2012;28:1070–8.
- Filardo G, Kon E, Pereira Ruiz MT, et al. Platelet-rich plasma intra-articular injections for cartilage degeneration and osteoarthritis: single- versus double-spinning approach. *Knee Surg Sports Traumatol Arthrosc* 2012;20:2082–91.
- Vaquero V, Plasencia MÁ, Arribas I, et al. Comparison of intra-articular injections of plasma rich in growth factors (PRGF-Endoret) versus Durolane hyaluronic acid in the treatment of patients with symptomatic osteoarthritis: a randomized controlled trial. *Arthroscopy* 2013;29:1635–43.
- Nurden AT. Platelets, inflammation and tissue regeneration. *Thromb Haemost* 2011;105 Suppl 1(Suppl 1):S13–S33.
- Tamaki T, Aoki N. Cross-linking of alpha 2-plasmin inhibitor and fibronectin to fibrin by fibrin-stabilizing factor. *Biochim Biophys Acta* 1981;661:280–6.
- Miyaki S, Lotz MK. Extracellular vesicles in cartilage homeostasis and osteoarthritis. *Curr Opin Rheumatol* 2018;30:129–35.
- Campbell KA, Saltzman BM, Mascarenhas R, et al. Does Intra-articular Platelet-Rich Plasma Injection Provide Clinically Superior Outcomes Compared With Other Therapies in the Treatment of Knee Osteoarthritis? A Systematic Review of Overlapping Meta-analyses. *Arthroscopy* 2015;31:2213–21.
- Sánchez M, Delgado D, Sánchez P, et al. Combination of Intra-Articular and Intraosseous Injections of Platelet Rich Plasma for Severe Knee Osteoarthritis: A Pilot Study. *Biomed Res Int* 2016;2016:1–10.
- Fiz N, Pérez JC, Guadilla J, et al. Intraosseous Infiltration of Platelet-Rich Plasma for Severe Hip Osteoarthritis. *Arthrosc Tech* 2017;6:e821–e825.
- Haleem AM, Singergy AA, Sabry D, et al. The Clinical Use of Human Culture-Expanded Autologous Bone Marrow Mesenchymal Stem Cells Transplanted on Platelet-Rich Fibrin Glue in the Treatment of Articular Cartilage Defects: A Pilot Study and Preliminary Results. *Cartilage* 2010;1:253–61.
- Filardo G, Madry H, Jelic M, et al. Mesenchymal stem cells for the treatment of cartilage lesions: from preclinical findings to clinical application in orthopaedics. *Knee Surg Sports Traumatol Arthrosc* 2013;21:1717–29.
- Jo CH, Lee YG, Shin WH, et al. Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a proof-of-concept clinical trial. *Stem Cells* 2014;32:1254–66.
- Roelofs AJ, Rocke JP, De Bari C. Cell-based approaches to joint surface repair: a research perspective. *Osteoarthritis Cartilage* 2013;21:892–900.
- Mishra A, Pavelko T. Treatment of chronic elbow tendinosis with buffered platelet-rich plasma. *Am J Sports Med* 2006;34:1774–8.
- Arirachakaran A, Sukthuyat A, Sisayanarane T, et al. Platelet-rich plasma versus autologous blood versus steroid injection in lateral epicondylitis: systematic review and network meta-analysis. *J Orthop Traumatol* 2016;17:101–12.
- Moraes VY, Lenza M, Tamaoki MJ, et al. Platelet-rich therapies for musculoskeletal soft tissue injuries. *Cochrane Database Syst Rev* 2014;CD010071. CD010071.
- Dupley L, Charalambous CP. Platelet-Rich Plasma Injections as a Treatment for Refractory Patellar Tendinosis: A Meta-Analysis of Randomised Trials. *Knee Surg Relat Res* 2017;29:165–71.
- Maffulli N, Florio A, Osti L, et al. Achilles Tendinopathy. *JBS Rev* 2014;2:1.
- Filardo G, Di Matteo B, Kon E, et al. Platelet-rich plasma in tendon-related disorders: results and indications. *Knee Surg Sports Traumatol Arthrosc* 2018;26:1984–99.



- 36 Schepull T, Kvist J, Norrman H, *et al.* Autologous platelets have no effect on the healing of human achilles tendon ruptures: a randomized single-blind study. *Am J Sports Med* 2011;39:38–47.
- 37 Kovacevic D, Rodeo SA. Biological augmentation of rotator cuff tendon repair. *Clin Orthop Relat Res* 2008;466:622–33.
- 38 Hurley ET, Lim Fat D, Moran CJ, *et al.* The Efficacy of Platelet-Rich Plasma and Platelet-Rich Fibrin in Arthroscopic Rotator Cuff Repair: A Meta-analysis of Randomized Controlled Trials. *Am J Sports Med* 2019;47:753–61. 363546517751397.
- 39 Warth RJ, Dorman GJ, James EW, *et al.* Clinical and structural outcomes after arthroscopic repair of full-thickness rotator cuff tears with and without platelet-rich product supplementation: a meta-analysis and meta-regression. *Arthroscopy* 2015;31:306–20.
- 40 Vavken P, Sadoghi P, Palmer M, *et al.* Platelet-Rich Plasma Reduces Retear Rates After Arthroscopic Repair of Small- and Medium-Sized Rotator Cuff Tears but Is Not Cost-Effective. *Am J Sports Med* 2015;43:3071–6.
- 41 Chahal J, Van Thiel GS, Mall N, *et al.* The role of platelet-rich plasma in arthroscopic rotator cuff repair: a systematic review with quantitative synthesis. *Arthroscopy* 2012;28:1718–27.
- 42 Greppi N, Mazzucco L, Galetti G, *et al.* Treatment of recalcitrant ulcers with allogeneic platelet gel from pooled platelets in aged hypomobile patients. *Biologicals* 2011;39:73–80.
- 43 Schipfinger G, Prüller F, Divjak M, *et al.* Autologous Platelet-Rich Plasma Preparations: Influence of Nonsteroidal Anti-inflammatory Drugs on Platelet Function. *Orthop J Sports Med* 2015;3:2325967115588896.
- 44 Jo CH, Shin JS, Lee SY, *et al.* ALLOGENEIC PLATELET-RICH PLASMA FOR ROTATOR CUFF REPAIR. *Acta Orthop Bras* 2017;25:38–43.
- 45 Hariri S, Safran MR. Ulnar collateral ligament injury in the overhead athlete. *Clin Sports Med* 2010;29:619–44.
- 46 Podesta L, Crow SA, Volkmer D, *et al.* Treatment of partial ulnar collateral ligament tears in the elbow with platelet-rich plasma. *Am J Sports Med* 2013;41:1689–94.
- 47 Deal JB, Smith E, Heard W, *et al.* Platelet-Rich Plasma for Primary Treatment of Partial Ulnar Collateral Ligament Tears: MRI Correlation With Results. *Orthop J Sports Med* 2017;5:232596711773823.
- 48 Hoffman JK, Protzman NM, Malhotra AD. Biologic Augmentation of the Ulnar Collateral Ligament in the Elbow of a Professional Baseball Pitcher. *Case Rep Orthop* 2015;2015:1–5.
- 49 Woo SL, Debski RE, Zeminski J, *et al.* Injury and repair of ligaments and tendons. *Annu Rev Biomed Eng* 2000;2:83–118.
- 50 Di Matteo B, Loibl M, Andriolo L, *et al.* Biologic agents for anterior cruciate ligament healing: A systematic review. *World J Orthop* 2016;7:592–603.
- 51 Seijas R, Ares O, Cuscó X, *et al.* Partial anterior cruciate ligament tears treated with intraligamentary plasma rich in growth factors. *World J Orthop* 2014;5:373–8.
- 52 Centeno CJ, Pitts J, Al-Sayegh H, *et al.* Anterior cruciate ligament tears treated with percutaneous injection of autologous bone marrow nucleated cells: a case series. *J Pain Res* 2015;8:437–47.
- 53 Andriolo L, Di Matteo B, Kon E, *et al.* PRP Augmentation for ACL Reconstruction. *Biomed Res Int* 2015;2015:1–15.
- 54 Beaufils P, Gaudot F, Drain O, *et al.* Mini-invasive technique for bone patellar tendon bone harvesting: its superiority in reducing anterior knee pain following ACL reconstruction. *Curr Rev Musculoskelet Med* 2011;4:45–51.
- 55 Seijas R, Cuscó X, Sallent A, *et al.* Pain in donor site after BTB-ACL reconstruction with PRGF: a randomized trial. *Arch Orthop Trauma Surg* 2016;136:829–35.
- 56 Seijas R, Rius M, Ares O, *et al.* Healing of donor site in bone-tendon-bone ACL reconstruction accelerated with plasma rich in growth factors: a randomized clinical trial. *Knee Surg Sports Traumatol Arthrosc* 2015;23:991–7.
- 57 McDermott ID, Amis AA. The consequences of meniscectomy. *J Bone Joint Surg Br* 2006;88:1549–56.
- 58 Ishida K, Kuroda R, Miwa M, *et al.* The regenerative effects of platelet-rich plasma on meniscal cells in vitro and its in vivo application with biodegradable gelatin hydrogel. *Tissue Eng* 2007;13:1103–12.
- 59 Zellner J, Taeger CD, Schaffer M, *et al.* Are applied growth factors able to mimic the positive effects of mesenchymal stem cells on the regeneration of meniscus in the avascular zone? *Biomed Res Int* 2014;2014:1–10.
- 60 Griffin JW, Hadeed MM, Werner BC, *et al.* Platelet-rich plasma in meniscal repair: does augmentation improve surgical outcomes? *Clin Orthop Relat Res* 2015;473:1665–72.
- 61 Blanke F, Vavken P, Haenle M, *et al.* Percutaneous injections of Platelet rich plasma for treatment of intrasubstance meniscal lesions. *Muscles Ligaments Tendons J* 2015;5:162–6.
- 62 Pujol N, Salle De Chou E, Boirensoul P, *et al.* Platelet-rich plasma for open meniscal repair in young patients: any benefit? *Knee Surg Sports Traumatol Arthrosc* 2015;23:51–8.
- 63 Betancourt JP, Murrell WD. Leukocyte-poor platelet-rich plasma to treat degenerative meniscal tear: A case report. *J Clin Orthop Trauma* 2016;7:106–9.
- 64 Assad S, Ahmad A, Kiani I, *et al.* Novel and Conservative Approaches Towards Effective Management of Plantar Fasciitis. *Cureus* 2016;8:e913.
- 65 Chiew SK, Ramasamy TS, Amini F. Effectiveness and relevant factors of platelet-rich plasma treatment in managing plantar fasciitis: A systematic review. *J Res Med Sci* 2016;21:38.
- 66 Franceschi F, Papalia R, Franceschetti E, *et al.* Platelet-rich plasma injections for chronic plantar fasciopathy: a systematic review. *Br Med Bull* 2014;112:83–95.
- 67 Tsikopoulos K, Tsikopoulos A, Natsis K. Autologous whole blood or corticosteroid injections for the treatment of epicondylopathy and plantar fasciopathy? A systematic review and meta-analysis of randomized controlled trials. *Phys Ther Sport* 2016;22:114–22.
- 68 Yang WY, Han YH, Cao XW, *et al.* Platelet-rich plasma as a treatment for plantar fasciitis: A meta-analysis of randomized controlled trials. *Medicine* 2017;96:e8475.
- 69 Beiner JM, Jokl P. Muscle contusion injuries: current treatment options. *J Am Acad Orthop Surg* 2001;9:227–37.
- 70 Hamid MS, Yusof A, Mohamed Ali MR. Platelet-rich plasma (PRP) for acute muscle injury: a systematic review. *PLoS One* 2014;9:e90538.
- 71 Andia I, Maffulli N. Muscle and tendon injuries: the role of biological interventions to promote and assist healing and recovery. *Arthroscopy* 2015;31:999–1015.
- 72 Borriore P, Fossati C, Pereira MT, *et al.* The use of platelet-rich plasma (PRP) in the treatment of gastrocnemius strains: a retrospective observational study. *Platelets* 2018;29:596–601.
- 73 Andia I, Sánchez M, Maffulli N. Platelet rich plasma therapies for sports muscle injuries: any evidence behind clinical practice? *Expert Opin Biol Ther* 2011;11:509–18.
- 74 Gigante A, Cianforlini M, Manzotti S, *et al.* The effects of growth factors on skeletal muscle lesions. *Joints* 2013;1:180–6.
- 75 Hamilton B, Tol JL, Almusa E, *et al.* Platelet-rich plasma does not enhance return to play in hamstring injuries: a randomised controlled trial. *Br J Sports Med* 2015;49:943–50.
- 76 Reurink G, Goudswaard GJ, Moen MH, *et al.* Rationale, secondary outcome scores and 1-year follow-up of a randomised trial of platelet-rich plasma injections in acute hamstring muscle injury: the Dutch Hamstring Injection Therapy study. *Br J Sports Med* 2015;49:1206–12.
- 77 A Hamid MS, Mohamed Ali MR, Yusof A, *et al.* Platelet-rich plasma injections for the treatment of hamstring injuries: a randomized controlled trial. *Am J Sports Med* 2014;42:2410–8.
- 78 Martinez-Zapata MJ, Orozco L, Balios R, *et al.* Efficacy of autologous platelet-rich plasma for the treatment of muscle rupture with haematoma: a multicentre, randomised, double-blind, placebo-controlled clinical trial. *Blood Transfus* 2016;14:245–54.
- 79 Zanon G, Combi F, Combi A, *et al.* Platelet-rich plasma in the treatment of acute hamstring injuries in professional football players. *Joints* 2016;4:017–23.
- 80 Bubnov R, Yevseenko V, Semenov I. Ultrasound guided injections of platelets rich plasma for muscle injury in professional athletes. Comparative study. *Med Ultrason* 2013;15:101–5.
- 81 Sánchez M, Anitua E, Delgado D, *et al.* Muscle repair: platelet-rich plasma derivatives as a bridge from spontaneity to intervention. *Injury* 2014;45 Suppl 4(Suppl 4):S7–S14.
- 82 Pas HI, Reurink G, Tol JL, *et al.* Efficacy of rehabilitation (lengthening) exercises, platelet-rich plasma injections, and other conservative interventions in acute hamstring injuries: an updated systematic review and meta-analysis. *Br J Sports Med* 2015;49:1197–205.