Platelet rich plasma – a revolution or just another treatment

Plazma bogata trombocitima – revolucionarna ili samo obična terapija

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Abstract. Musculoskeletal injuries are the most frequent reason for athletes being away from sports competitions. Modern sport strives to return athletes to full competition rhythm after injury as soon as possible. Accordingly, new therapeutic discoveries have been found whose function is to accelerate the healing process with as high tissue quality as possible. The current musculoskeletal system injury management methods include protection, rest, ice, compression, elevation, NSAID, physiotherapy, hyperbaric oxygen therapy, prolotherapy injections and corticosteroid injections. The last resort is surgery. Nevertheless, conservative treatment is preferred because surgical treatment requires longer recovery and there is a possibility of developing complications. The new and still insufficiently investigated non-operative treatment is platelet rich plasma (PRP). PRP is a simple product that is derived from the patient's venous anticoagulated blood and it possesses a concentration of platelets which is 4 to 6 time bigger. The growth factors released from granules of the platelets include the transforming growth factor (TGF-β), platelet-derived growth factors (PDGF-AB and PDGF-BB), the insulin-like growth factor (IGF), vascular endothelial growth factors (VEGHs), epidermal growth factors (EGFs) and the fibroblast growth factor (FGF). PRP is used for the treatment of acute muscle injuries, tendon injuries, ligament injuries and chondral lesions. Although PRP is suggested as a safe and harmless product, its efficiency is still a matter of discussion, since there are not enough studies that could be evaluated and mutually compared; however, generally speaking, it is accepted that the PRP can accelerate the healing response and stimulate athletes' recovery from some well indicated injuries.

Key words: athletes; chondral lesions; growth factors; muscle injuries; platelet rich plasma; tendon injuries

Sažetak. Ozljede mišićno-koštanog sustava najčešći su razlog udaljavanja sportaša sa sportskih borilišta. Moderni sport teži tome da se sportaše što prije nakon ozljede vrati u puni natjecateljski ritam. Tragom toga dolazi se do novih terapijskih otkrića kojima je glavna fukcija ubrzati procese cijeljenja sa što kvalitetnijim tkivom. Trenutno korištene metode zbrinjavanja ozljeda mišićno-koštanog sustava uključuju zaštitu, odmor, led, kompresiju, podizanje ozlijeđenog uda, nesteroidne protuupalne lijekove, fizikalnu terapiju, hiperbaričnu terapiju kisikom, proloterapiju i injekcije kortikosteroida. Posljednje rješenje je kiruški zahvat. Unatoč svemu, teži se konzervativnom liječenju jer kiruško liječnje zahtijeva duži oporavak te postoji mogućnost komplikacija. Nova i još nedovoljno istražena nekiruška metoda jest plazma obogaćena trombocitima. Radi se o jednostavnom proizvodu koji se dobiva iz venske nekoagulirane krvi pacijenta i koji sadrži 4 do 6 puta veću koncentraciju trombocita. Čimbenici rasta koje otpuštaju granule trombocita su transformirajući čimbenik rasta (TGF-β), čimbenik rasta podrijetlom iz trombocita (PDGF-AB i PDGF-BB), inzulinu sličan čimbenik rasta (IGF), vaskularni endotelijalni čimbenik rasta (VEGHs), epidermalni čimbenik rasta (EGFs) i čimbenik rasta fibroblasta (FGF). Koristi se za liječenje akutnih ozljeda mišića, ozljeda tetiva, ozljeda ligamenata i hondralnih lezija. Iako se liječenje plazmom obogaćenom trombocitima preporuča kao siguran i bezopasan proizvod, njegova učinkovitost i dalje ostaje predmet rasprava, s obzirom da ne postoji dovoljno istraživanja koja bi se mogla evaluirati i međusobno usporediti. Međutim, općenito je prihvaćeno da plazma obogaćena trombocitima može ubrzati proces zacjeljivanja i stimulirati oporavak sportaša kod dobro indiciranih ozljeda.

Ključne riječi: čimbenici rasta; hondralne lezije; ozljede mišića; ozljede tetiva; plazma obogaćena trombocitima; sportaši

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SPORTS RELATED MUSCULOSKELETAL INJURIES

Musculoskeletal injuries are the most frequent reason for long lasting pain and physical disability that affects the life of hundreds of millions of people around the world according to the World Health Organization (WHO)[1]. Among the population of professional athletes, these injuries represent a major problem. Skeletal muscles are the most affected ones and make up for 55 % of all musculoskeletal injuries[2]. Muscle lesions such as contusions and strains are the most common injuries of the skeletal muscles, and they constitute as much as 90 % of all sports related injuries[3]. Up to 45 % of musculoskeletal system injuries involve soft tissue injuries such as ligament and tendon injuries.[4] Depending on the time needed for their development, injuries are divided into two types, acute and chronic injuries[5]. Acute musculoskeletal injuries are a result of a single, traumatic experience that usually follows high energy trauma, such as muscle contusion or rupture and ligament sprain or tear. Chronic musculoskeletal injuries are a result of a repetitive micro trauma or overuse of a structure, for example a tendon that can result in tendinopathy, such as Achilles, patellar, elbow or rotator cuff tendinopathy. Regardless of the mechanism of injury, all injuries pass through the well-known phases of healing, with slight differences in the time of healing, the length of each phase and the mediator molecules that play a significant role in the whole process of healing[6-8].

PRP is a relatively new, safe and simple conservative method for treatment of sports related musculoskeletal injuries. PRP is administered in cases of acute muscle, tendon and ligament injuries, as well as for chondral lesions.

In the life of a professional athlete, these injuries result in the inability to train and participate in activities, and further on lead to a variety of problems that accompany the athlete's return to an adequate level of efficiency in training that can guarantee giving their maximum in competition. These injuries are very often accompanied by long lasting and persistent pain that incapacitates players in the long run[9]. It is of a great importance for an athlete to be able to return as soon as possible to full training and competition rhythm. Clubs that pay large amounts of money for players have an especially large interest in that matter because they want to have players who are well trained and constantly at a high level of performance during the competition period, no matter the circumstances. One has to be aware that professional athletes are obliged to make many sacrifices in their private lives so that their physical performance would not be affected.

Current management methods of musculoskeletal system acute injuries are commonly known as PRICE, which stands for protection, rest, ice, compression and elevation of the affected limb, all of which are of an extreme importance especially after injury and must be applied as soon as possible[3,10-12]. Other methods of treatment also applicable in practice are anti-inflammatory medications (NSAID), physiotherapy under strict supervision of the physiotherapist, hyperbaric oxygen therapy, prolotherapy injections[13-16] and in some cases corticosteroid injections. In situations when all conservative treatments fail to give a result, in refractory cases and chronic types of injuries surgical intervention is required. However, surgical treatment has some possible complications. An especially important disadvantage of surgical intervention is that recuperation of an athlete is longer, thus also prolonging the athlete's time away from training and competition. The question always remains whether the athlete will be able to return to the same level of performance as before surgery. Even if complete physical recuperation is achieved, in some cases the athlete remains with a mental barrier caused by the fear of being injured again and being kept away from competing. So, conservative therapy and its methods are still more preferred, since they shorten the rehabilitation time and bring the athlete sooner back into play. The need for non-operative treatment has developed new management modalities and the need for surgical treatment remains the last resort therapy.

One of the new and still investigated modalities of non-operative treatment is platelet rich plasma (PRP). This kind of treatment is still wrapped with mystery and assumptions, so everybody still interprets it in their own way. The authors hope to demystify and clarify the use of PRP treatment.

The aim of this review is to evaluate the effect of the relatively new, simple and safe option of non-invasive conservative treatment with PRP injections in sports-related injuries discussing all current world literature.

PLATELET RICH PLASMA

Platelet rich plasma (PRP) is a product derived from the patient's own venous blood and prepared with an increased level of concentration of the platelets (Figure 1). A typical blood specimen consists of 93 % erythrocytes, 6 % platelets and 1 % leukocytes[17]. Platelets were first described and further investigated in 1842 by the French physician Alfred Donné[18]. Instantly after an injury that causes bleeding, platelets are the first cells that arrive at the location of the injury, are activated, and then release various types of growth factors by degranulation of α granules that further on activate the whole cascade of the healing process. Their main functions include hemostasis, development of the connective tissue and revascularization, and these were the functions that were mostly examined in the past[19]. However, in the latest examinations, other roles and effects of platelets were researched and further investigated, especially their growth factors. There are a great number of growth factors with different roles and effects that they provoke but they all, considered together, speed up the process of wound healing[20]. A normal number of platelets is between 150,000 and 450,000 cells per microliter of blood, and concentrations of platelets five or more times higher are considered effective to cause accelerated healing. The ideal amount of platelets still remains open for discussion and should be more closely investigated in the future. PRP should be of such consistence that it is composed of a decreased level of erythrocytes and an increased level of platelets, up to as much as 94 % of the concentration, which is actually a diverse proportion of a regular blood sample. The question of leukocyte concentration is still a matter of discussion and should also be further investigated. The growth factors that are released from activated platelets include various factors, such as the transforming growth factor (TGF-β), platelet-derived growth factors (PDGF-AB and PDGF-BB), the insulin-like growth factor (IGF), vascular endothelial growth factors (VEGHs), epidermal growth factors (EGFs) and the fibroblast growth factor (FGF)[21-23]. TGF-β1 and PDGF appear to be two most important mediators that provoke proliferation of mesenchymal cells and in the end lead to the formation of a new connective tissue, leaving a cicatrix. While PDGF is important in the early stages of healing, TGF-β1 is significant for production of collagen in the extracellular space and in the later phases of healing[24]. VEGF and FGF-2 are, among other factors, important mediators that play a key role in revascularization of the newly formed connective tissue.

Figure 1. The preparation of the patient for drawing venous blood; 10 cc of venous blood is necessary for the preparation of platelet rich plasma (PRP).

Figure 2. The syringe with venous blood is placed in centrifuge at 1500 rpm for 5 minutes

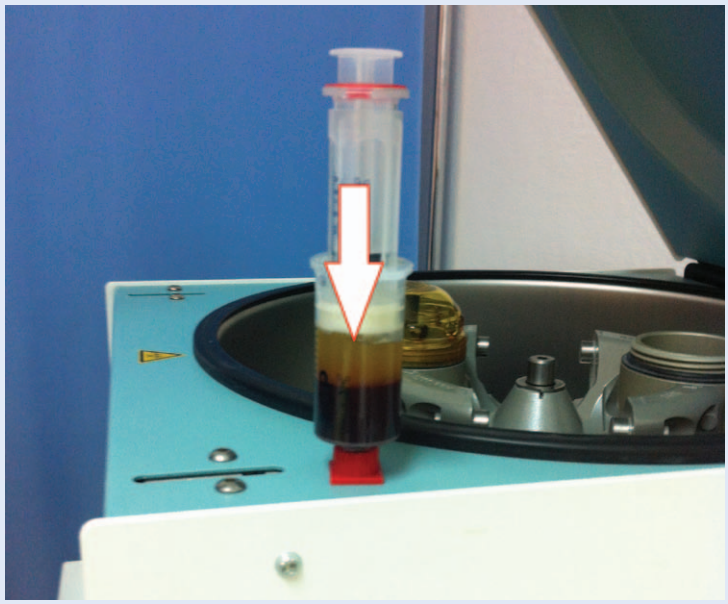

Figure 3. After applying the centrifuge, the supernatant (yellow) is seen in the upper layer; it is distinct from the red blood cells in the lower layer of the syringe. The supernatant is separated in the syringe system and is ready to use.

The role of IGF is also important, but controversial findings have been reported.

Injections of PRP were first recorded in practice in 1987 in an open heart surgery[25]. Over the past years, they have spread in all kinds of specialities, such as otolaryngology, oral and maxillofacial surgery, and general surgery. In sports related injuries, PRP became popular in 2009, when the ankles of two Pittsburgh Steelers were treated with PRP injections just before the victory at the Super Bowl[26]. A whole article about this magical drug was published in New York Times and the story was instantly widespread so, without any further investigations, PRP became accepted in sports medicine[27]. The World Anti-Doping Agency (WADA) forbid intramuscularly applied injections of PRP in professional athletes in 2010, since it was suspected that it may enhance their performance because of its high concentration of growth factors. However, in 2011 the prohibition of PRP was canceled because there was not enough information on the systemic influence of PRP, but the application of only growth factors still remains forbidden[28].

PRP is a simple product that is derived from the patient's venous anticoagulated blood. The blood specimen is then subjected to two processes of centrifugation (Figure 2), in the first of which erythrocytes and leukocytes are separated from the plasma with platelets, while in the second the platelets are concentrated and separated from the plasma, which normally contains a low number of platelets[29]. The concentration of the platelets should be 4 to 6 times bigger than the baseline concentration[4] (Figure 3). Afterwards, plasma rich in platelets is activated either with thrombin, calcium chloride or collagen type I, since clotting leads to degranulation of growth factors[29]. When using thrombin as an activation material, 70 % of the growth factors are activated in the first 10 minutes, and almost all of them are activated within 1 hour[30]. When using calcium chloride as an activation material, the length of activation of platelets is significantly longer, and the growth factors are released more slowly within 7 days. The third option for activation is collagen, which has shown similar effects as thrombin, but further *in vivo* examinations need

to be made[31]. For the moment, there are several variations of PRP preparations depending on different manufacturers on the market. They vary in the amount of blood that should be taken, the anticoagulant material (usually acid citrate dextrose), the activation material, the final optimal volume, the achieved concentration of platelets and the time needed for growth factors release, so the exact quantifying of PRP method stays still undefined[4].

CONDITIONS IN WHICH PRP IS ADMINISTERED

A whole variety of studies exists in literature, from animal studies, case reports and smaller series of cases, which suggest how PRP is a simple, safe and minimally invasive procedure that can be applied in all kinds of conditions[29,32] (Figure 4). Although many of these studies report good results of PRP management, their results are limited due to absence of a control group, too small sample size or non-standardized PRP procedure preparations, and thus cannot be mutually compared. For the time being, PRP management for conditions affecting the musculoskeletal system can be divided into 4 groups in which this kind of management is recommended.

Figure 4. The application of PRP into the knee joint.

Acute muscle injuries

Muscle injuries are a result of a single direct trauma or eccentric load applied on the muscle in contraction. These trauma mechanisms cause different injuries and they vary from contusion with unharmed integrity of the muscle to smaller or bigger tears of the muscle. In most cases skeletal muscle injuries in athletes involve hamstrings, quadriceps and gastrocnemius. All these injuries can keep an athlete away from training and competition rhythm for a couple of weeks. This is a major problem of professional sport, where all possible efforts along with technological achievements are invested in order to reduce the number of injuries in professional athletes. However, if an injury occurs, all efforts are taken to reduce the recovery and healing time. Recovery has to be instant and complete within only a brief period of time away from training and competing. As all other tissues, muscles heal through the well-known phases that include first inflammation, then proliferation and in the end remodeling of the tissue. The time of healing depends on various factors, for example the type of injury and its severity, the treatment method applied instantly after the injury, and individual characteristics of each organism to be healed[29].

Apart from the standard management treatment with PRICE, PRP has been proposed to deal with acute injuries of skeletal muscles.

In a recent animal study carried out on rats, PRP injections were administered on the site of the multiply loaded, eccentric injury of tibialis anterior muscle. The outcome was very satisfying, since the time needed for recovery was shortened from 21 days to 14 days[33]. The efficiency of PRP injections was higher in the group with repetitive muscle trauma than in the group with single trauma, which was explained by myogenesis that appears in repetitive trauma and is ena-

bled by the growth factors, which are concentrated in PRP. In another animal study, autologous conditioned serum (ACS) was injected into the injured gastrocnemius muscle of the mice after injury using several consecutive injections, and it caused histologically proven myofiber regeneration[34].

One human case study was performed involving 14 professional athletes with acute muscle injuries. Conducted with the help of ultrasound, PRP injection was administered directly into the location of the muscle tear. The outcome was satisfying because the time for complete return to play was shortened, and thus the authors concluded that PRP can be helpful in sports-related injuries. Its limitation lies in the retrospective characteristic of the research and the absence of a control group to which the results could be compared[35]. Another human study that was performed evaluating PRP injections in proximal hamstrings injuries of 15 patients suggested that PRP method is a superior method to the traditionally applied conservative management. All patients treated with PRP after unsuccessful conservative treatment presented with a better outcome due to the reduced level of pain and the ability to return to the normal range of activities as before the injury, while the group of patients treated with traditional conservative methods had no important reduction in pain or in the measured parameters[36].

Although most studies report good results of PRP management, their results are limited due to the lack of standardization. There is a true need for clinical studies with longer follow-up that could determine precise indications, PRP levels and application protocols, which still depend much on the manufacturer.

Some authors examined how PRP inducts fibrotic healing seen in histological samples of acutely injured muscles, since it levels up the concentration of TGF-β, for which basic science studies showed that in vitro can cause fibrosis. In one animal study, PRP injections were combined with the usage of Losartan, an antihypertensive drug that blocks angiotensin (II) receptors. The study showed a decrease of fibrosis and an increase in vascularization in a rat muscle contusion in case of combined PRP and Losartan therapy[37]. The main purpose of this combined therapy is to develop as many muscle fibers as possible in the place of the injured muscle, with as little as possible amount of fibrosis or scar tissue, which is functionally less qualitative tissue. However, since Losartan is an angiotensin (II) receptor blocker, its side effect, when not used in the therapy of hypertension but in normal healthy population, is lowering of the blood pressure. Also, anti-TGF-β factors such as suramin, γ-interferon and relaxin are mentioned as possibly active products in diminishing the induction of fibrosis[38,39]. These studies show how PRP combined with anti-TGF-β factors can act against the undesirable effect of fibrosis and induce desirable effects of angiogenesis and myogenesis through inhibition of TGF-β[5].

Tendon injuries

In the population of athletes, injuries of the tendon are a very common condition that can result in long-lasting disability and inability to compete. These injuries include acute lesions and chronic degenerative processes. An acute lesion of the tendon is usually a result of one single trauma, while chronic tendinopathy happens in the hypovascularly changed tendon tissue due to multiple micro traumas that result in scar formation of the injured tendon[40]. The process of healing is very complex, the time for full recovery is long and the healing tissue of the tendon can never be mechanically as durable as a tendon lesion-free tissue. Conservative treatment involves NSAID and steroid injections as well as local anesthetic injections. The efficiency of these modalities of management still remains questionable[41-45]. PRP is a new modality of management for tendon injuries such as Achilles tendopathy, plantar fasciitis, elbow tendinopathy, especially lateral epicondylitis, and the jumpers knee. Several studies showed good effects of PRP in tendon injuries. In vitro studies suggest that autologous PRP could be effective in the management of an injured tendon because, in the culture of human tenocytes, it stimulates proliferation of cells and pro-

duction of angiogenic factors, especially VEGF and HGF, during the period of healing[46]. In an animal study, a similar effect of improved tendon healing, especially in the first stages, was seen after one injection of PRP in a rabbit patellar tendon injury, due to over-expression of IGF-1[47].

A human study consisting of 20 patients with patellar tendinosis was conducted. Patients with long lasting pain and disability for an average time of 20 months received 3 doses of PRP injections in the injured tendon every 15 days, and afterwards better functional results in measurable scores were recorded in a half-year period of follow-up[48].

A human study administering PRP was performed in a case of lateral epicondylitis in which significant reduction of pain after 2-year period of follow-up was achieved after injecting one dosage of PRP[49]. Another human study comparing PRP and corticosteroid injections in chronic lateral epicondylitis concluded that patients treated with PRP had reduced pain and increased level of function, after 6 months, 12 months and even after a long-term follow-up, namely, after 2 years[50,51]. On the other hand, one human study comparing PRP, corticosteroid and saline injections in lateral epicondylitis showed no significant difference in pain relief between these three modality treatments after 3 months of consistent follow-up[52].

Regarding chronic Achilles tendinopathy, a study was performed comparing PRP injections to placebo (saline injections) and no significant difference in pain or function was seen between the examined groups after 6 months and the entire year follow-up[53]. However, in an acute setting of the injury and in athletes undergoing a surgical repair of the tendon, PRP was administered intraoperatively and showed a very good outcome, since the patients were able to achieve full range of motions sooner, had less wound-associated healing complications, and continued with previous activities sooner than those treated with isolated surgical intervention[54,55].

In dealing with chronic rotator cuff tendinopathy, PRP injections showed no significant difference in pain, function, quality of life and range of motions compared to the placebo group, which was treated only with physical therapy[56]. However, another research study suggests that intraoperative injection of PRP could possibly be effective to improve healing of rotator cuff structures after surgical intervention, since many cases resulted in an undesirable surgical outcome which is not directly in correlation with the surgical skills and experience of the surgeon[29].

Studies evaluating the benefit of PRP with arthroscopic rotator cuff repair showed no major improvements of either clinical or functional results for full-thickness rotator cuff tears[57-60]. However, in cases of small and medium cuff tears, a decreased number of re-tears was seen in patients treated with PRP modality of treatment[61].

Ligament injures

Besides tendon and muscle injures, ligament injuries are extremely common in sports medicine. Most of them are treated conservatively, such as the injury of the medial collateral ligament (MCL), while some need surgical intervention, such as the anterior cruciate ligament (ACL), because of its small healing potential[62-64] due to poor vascularity[65-67].

In a porcine model, PRP in the form of collagen-PRP hydrogel was used to stimulate healing of ACL repair and reconstruction after transaction. A major advancement was recorded regarding load and linear stiffness in the 4-week follow-up, so the authors point towards PRP usage since it helps in the early phases of healing[68]. Also, the same group of authors tested a collagen-PRP hydrogel and its influence on the ACL injury model in a canine, and found better healing abilities[69].

The effect on an injured ACL and the benefit during surgical repair has also been investigated.

In a prospective, double-blinded clinical study, a local platelet gel was administrated on the ACL graft, and after 4 to 6 weeks period after the reconstruction the authors examined the process of revascularization of the ACL graft with the help of contrast-enhanced magnetic resonance imaging (MRI). The improvement was noted in the aspect of the vascularization in the location of the osteoligamentous interface, but no signs of vascularization were seen in the intrarticular area of the ACL graft[70]. In another prospective, rand-

omized study, the same authors tested the effect of platelet-derived growth factors on knee stability after reconstructive procedure of the ACL in 50 patients. Remarkably improved results of anteroposterior knee stability were recorded with arthrometer in 25 patients with this kind of management compared to the control group of other 25 patients after 6 months of follow-up[71].

Chondral lesions

Articular cartilage is constantly exposed to all kinds of trauma and in the end the damage can be definite and result in osteoarthritis. Very poor capacity of regeneration of the cartilage is still a daring question for all orthopedic surgeons[72,73].

The growth factors released from α granules of the platelets regulate the production of hyaluronic acid and have a great influence on the cartilage and on the whole joint protection[74]. Intrarticular injection of the PRP seems to be effective in maintaining the homeostasis of hyaluronic acid concentration[75].

Studies showed a satisfying outcome in dealing with chondral lesions in athletes using PRP for the revival of the articular cartilage[35]. Also, authors recapitulated how local treatment with PRP is harmless and without amplification of the systemic values of growth factors[35]. In a clinical study involving 100 patients (115 knees) with degeneratively changed cartilage (patients had Kellegren scoring system 0-IV), PRP was administrated intrarticularly in the knee. The condition of patients before the treatment, after the treatment, 6 months and one year after the treatment was compared. At the end of the management, the results were remarkably better, remaining stable after the 6-month follow-up, but becoming worse after 1-year follow-up. The authors suggest that PRP management is harmless, with a possibility to ease pain and enhance knee function, especially in a younger population with low-grade cartilage lesions[76]. Also, in a prospective, randomized study regarding treatment of early lesions of osteoarthritis of the knee in 93 patients, intraarticular PRP injections were suggested as an approved management modality. There was a remarkable decrease in pain and enhancement in function after a whole year follow-up, and although after 2 years the values of measured scores aggravated, they were still better than the initial values at the beginning of the treatment[77].

One case report presented a case in which PRP was administered in the location between the lesion and a previously fixated loose chondral fragment (> 2 cm) from the medial femoral condyle in a young soccer player. The process of the articular cartilage lesion healing was shortened and quick return to athletic activity without any symptoms was achieved[78].

DISCUSSION

Sports related musculoskeletal injuries are very common, so every athlete's quick and efficient recovery and reduced time away from competing are the main concerns and obligation of a medical team. Every minute that passes with an athlete out of training represents a big loss for the player as well as for the whole team. In treating musculoskeletal injuries, conservative methods are still a priority since surgical intervention in most cases keeps an athlete away from training for a longer period of time and can involve a variety of complications, such as the risk of infection, damage of neurovascular structures, thrombosis and complications connected to the wound healing process. Current conservative methods are still focused on traditional management with protection, rest, ice, compression and elevation which do help, but do not speed up the process of healing as much as everyone would prefer. Thus, the search for some other conservative methods that would accelerate healing is a very challenging issue. A method that could match these criteria is PRP.

PRP is a relatively new, safe and simple conservative method for treatment of musculoskeletal injuries. Since this is a modality of management that is minimally invasive, it is very interesting in sports medicine and sports related injuries. It is suggested as a safe treatment, since it is an autologous blood-derived product, with a low risk of rejection. There are minimal negative side effects, especially compared to other modalities of conservative treatment. It has been reported that NSAIDs prevent healing when used in a longer period of

time, and are recommended to be used between 3 and 7 days since in that period they reduce pain and edema, increase joint amplitude and load-bearing ability, but their long-term usage has the opposite effects[79,80]. Corticosteroid injections, on the other hand, can accelerate the recovery time in athletes, but in comparison to PRP can cause slowed long-term soft tissue healing or no healing at all, further tendon degeneration with increased risk for possible rupture because they prevent linking of the collagen[79-84]. Other known side effects are subcutaneous fat tissue atrophy and hypopigmentation of the skin[36]. In addition, PRP is a method that can be easily prepared at the place where the patient is being treated and does not require large preparations or special training for its application[29]. Some possible side effects could be complications regarding initial blood taking, such as hematoma, thrombosis of the vein or possible infection. Similar complications could occur on the site of PRP injection, in the form of minor bleeding, damage of soft tissues during needle injection or also possible infection (36 – Wetzel et al., 2012). There were some theoretical concerns indicating that an increased level of growth factors could possibly have some systemic effects as well as a cancer-like effect[29], but these theories were rejected due to one research study performed on 10 elite athletes. The study suggested that one intramuscular injection of PRP does not particularly level up systemic values of growth factors, except for TGF-β2, and especially not the systemic value of IGF-1, and therefore has no cancer-like effect[85,86].

Regarding the cost-effective aspect of treatment with PRP, it is recorded that in a short term its application is not as cost-effective as, for example, that of corticosteroid injections. However, taking into account situations in which corticosteroid injections failed to give an adequate response and often proceeded to surgical treatment with increasing treatment costs, in the end the costs level out and have no significant difference compared to PRP[50]. Also, it is a method that is more cost-effective than, for example, gathering stem cells[29].

Currently, PRP has proved effective in cases of acute muscle injury, able to accelerate athletes' return to adequate activity.

In cases of tendinopathy, various effects were seen. Good results were reported in studies examining lateral epicondylitis, since reduction in epicondylar pain after a 2-year follow-up was reported[49]. Also, studies examining lateral epicondylitis and comparing PRP to treatment with corticosteroid injections showed better results of PRP, with reduced pain and increased functional scores after 6 months, 12 months and 2 years of follow-up[50,51]. One study showed no difference when comparing PRP, corticosteroid or saline injections after 3 months of consistent follow-up[52]. Considering the available literature, we believe that PRP can be the selected therapy for treating lateral epicondylitis. In an acute setting of Achilles tendinopathy in athletes undergoing a surgical repair of the Achilles tendon, good results were also reported, but no significant difference was seen in cases of chronic tendinopathy of the Achilles tendon in a study comparing results after 6 months and 1 year of follow-up[54,55]. The use of PRP for treating the Achilles tendon injuries has not been justified given the results of conducted research. Also, in dealing with chronic rotator cuff tendinopathy, PRP injections showed no difference compared to the placebo group[56]. No benefit was reported when using PRP during arthroscopic full-thickness rotator cuff repair, but potential benefit was suggested for small- and medium-sized rotator cuff tears[29,61]. However, if the cost of PRP and the potential benefit for small- and medium-sized rotator cuff tears are compared, then conservative treatment, which has a proved efficiency, would be the preferred choice, especially in senior population. In case of arthroscopic reconstruction, surgical procedure combined with physical therapy and NSAID would be used for the mentioned injuries.

The effect of PRP on an injured anterior cruciate ligament and the benefit after 4 to 6 weeks after surgical repair showed improvements in vascularization in the osteoligamentous interface, but no any signs of revascularization in the intrarticular part of the graft were recorded with contrast MRI[70]. Also, remarkably improved anteroposterior knee stability was recorded after a 6-month follow-up after a PRP treatment[71]. In ACL reconstruction, PRP can be used as a supportive thera-

py in terms of faster and better recovery together with compulsory and strict post-surgery rehabilitation protocols; however, we consider that further research is necessary in order to recommend it as treatment. The cost-benefit ratio is perhaps justified only in professional athletes but for making any conclusions, precisely defined double blinded prospective studies are necessary.

In dealing with chondral lesions in athletes, PRP was reported as being beneficial because of the reduction in pain and improved functional scores[35,76]. Regarding the treatment of early osteoarthritis knee lesions, intra-articular PRP injections were suggested as a valid management modality, since improvement was noted in pain and function after 1-year follow-up, and although after 2 years the values of measured scores declined, they were still above the levels of pretreatment values[77]. We believe that PRP is a justified treatment in younger population and in athletes with chondral lesions, especially grade I and II ones, and in case of the first signs of osteoarthritis. Based on the available literature, it has been identified that it reduces pain and improves the functional scores. However, the authors consider that studies with a longer follow-up are required, as well as patients with precisely determined lesion grades, defined PRP levels and application protocols in order to be able to give recommendations.

Consequently, although PRP is suggested as a safe and harmless product, its efficiency is still a matter of discussion, since there are not enough studies that could be evaluated and mutually compared. Generally speaking, however, it is accepted that PRP can accelerate the healing response and stimulate an athlete's recovery from some well indicated injuries.

Although many of the above-mentioned studies state good results of PRP management, their results are limited since in some cases they did not have a control group, the sample size of the examined groups was not big enough or did not have standardized PRP procedure preparations and thus cannot be compared. So, there is a true need for more clinical studies that can overcome these problems and establish a PRP management as a truly safe and scientifically approved method.

This review emphasizes that there is still an enormous lack of standardization in the types of preparations of PRP, depending on different manufactures on the market. They vary in the amount of blood that should be taken from the patient, the use of anticoagulant material, the activation material, the final optimal volume, the achieved concentration of platelets, the leukocyte concentration and the time needed for growth factors release, so the exact quantifying of PRP method remains still undefined and requires further investigations.[4] Future standardization could provide more consistent answers on the real effect of PRP and indications in which this method could be applied. The necessity of developing a prospective controlled trial study is extreme and could clarify the promotion of the healing process in both soft tissues and bones.

CONCLUSION

Professional sport is becoming even more governed by sponsors, marketing and affluent owners which cause the loss of its true purpose. Athletes are being made super humans and models at the expense of their own health. However, awareness is slowly being raised about this issue and more investment is made into medical providers and staff who monitor professional athletes. Today, professional clubs have their own research laboratories and hospitals that take care of their millions-worth investments. In the population of professional athletes, musculoskeletal injuries represent a major problem. Conservative methods are still a priority in the treatment of such conditions, since surgical methods in some cases can hold an athlete outside of training for longer periods of time. A relatively new method of minimal invasive medical management is PRP. However, its efficiency is still a matter of discussion. Although many of the above-mentioned studies state good results of PRP management, their results are limited, and the main problem is lack of standardization.

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