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Platelet-rich plasma in treatment of acute lesions and chronic disease of forearm, wrist and hand

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Abstract

Introduction: The aim of this study is to compare the efficiency of Platelet-rich plasma (PRP) in the treatment of acute lesions and chronical disease of bones, joints and nerves from forearm, wrist and hand. **Material and Methods:** articles published in English between 2008 and 2018 from medical literature were selected. **Results:** when it comes to acute lesions three articles were found; one about the using of PRP in distal radius fractures and the two about the infiltration of PRP in the complete neurotmesis of radial nerve or in digital nerve incomplete section. In chronic conditions only one article about trapeziometacarpian (TMC) osteoarthritis (OA) was found, and three articles about a median nerve compression in carpal tunnel syndrome (CTS). **Conclusions:** 1.The medical literature contains few publications regarding the efficiency of PRP in treatment of traumatic lesions and chronic disease of forearm, wrist and hand. 2. In chronic conditions the favorable outcomes after the PRP injection are obtained only in the first stage of the disease, in advanced stages the surgical treatment is mandatory.

Key words: *platelet –rich plasma, acute lesions ,chronic disease , hand and wrist, treatment of OA,*

Introduction

Orthobiologics is a relatively new science that involves application of naturally found materials from biological sources (for example, cell-based therapies) and offers exciting new possibilities to promote and accelerate bone and soft tissue healing. Platelet-rich plasma (PRP) is defined as a portion of the plasma fraction of autologous blood having a platelet concentration above baseline. A typical human blood specimen contents 93% red blood cells, 6% platelets and 1% white blood cells [1]. Following injury that causes bleeding, platelets are activated and aggregate together to release their granules containing growth factors that stimulate the inflammatory cascade and healing process [1].Platelets are responsible for hemostasis, construction of new connective tissue and revascularization [2]. PRP is a sample of autologous plasma twice centrifuged which is beneficial in bone and soft tissue healing for its high concentration of growth factors and cytokines that stimulate cell proliferation and extracellular matrix protein production [3].The first phase consists of an initial soft spin between 1,200 to 1,400 RPM with a relatively low gravitational force in which plasma and platelets are separated from red blood cells and white blood cells (RBCs and WBCs). The second phase or hard spin (4000-7000 RPM) is performed to further concentrate the platelet-rich and platelet-poor plasma (L-PRP and P-PRP) [4]. The protein in PRP contains growth factors of different type: platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), transforming growth factor (TGF – β), insulin like growth factor (IGF), which initiate cell multiplication and cell migration to the affected area [4].Thrombine and/or calcium chloride is necessary to catalyze the convention of fibrinogen to fibrin, but also to induce platelets to produce growth factors. Some data suggests that exogenous thrombine activation of PRP may actually diminish its ability to induce bone formation, compared with non-thrombine activated PRP [5]. Depending on the presents or absence of leucocytes, the smaller or bigger amount of fibrin and the standard procedure of obtaining, there are several types of PRP: Leucocyte-poor or pure platelet-rich plasma (P-PRP), Leucocyte and platelet-rich plasma (L-PRP), Leucocyte – poor or pure platelet – rich fibrin (P-PRF), Leucocyte and platelet – rich fibrin (L-PRF). A high density fibrin clot can serve as a biological healing matrix, by supporting cell migration and cytokine release, expending the range of its potential applications greatly.

The influence of the leucocytes and its potential benefits should be carefully analyzed because it could explain many controversial data from the literature [6]. We believe that there is need for a first step to clarify the biotechnological applications in medical practice and the further progress depends on the accuracy of this matter.

Materials and methods

Using the searching engines like Pubmed, Medscape and Scopus, were selected only the English articles published between 2008-2018. Only those articles were analyzed which contained the PRP effects in the treatment of bone and nerves disease, of forearm, wrist and hand. The study tried a comparison between the role of PRP in trauma (distal radius fracture) and the chronical disease like osteoarthritis (OA). In a similar way, there were analyzed the PRP effects in radial nerve section, in digital nerve lesion and in chronical disease of median nerve (compression) in carpal tunnel syndrome.The followed parameters were the pain reduction, increasing range of motion (ROM), improvement grip of strength and early return to daily activities. The patients were followed-up for 3 and 6 months post injection and those with a nerve section till 9, and 14 months respectively. The analyzed studies summed up a number of 14 patients in case of bone diseases and 117 in the nerve disease.

A number of 30 patients with intra-articular distal radius fracture without comminution have undergone minimal invasive surgical interventions. Under guide of fluoroscopy (C-Arm) closed reduction and percutaneous pinning of fracture were done. Then, the patients, belonging to the case group (14 patients), underwent injection of PRP in radiocarpal joint. Then short arm cast was applied as routine. Meanwhile the remaining 15 patients (control group) didn't receive anything. The cast was on for 6 weeks. The PRP injection was prepared by a sample of 10 cm^3 of venous blood taken from patients' hand. The sample was centrifuged with speed of 1500 rpm for 5 minutes. About 3-5 ml was extracted from the sample and it was injected in the patients' radiocarpal joint from dorsal approach. All injections in the radio carpal joint were performed in less than 20 minutes after sampling. Both group of patients were followed up after 2 and 6 weeks by taking radiography, then after cast removal they were still closely followed up and the rehabilitation began at 3 and 6 months post operatory. The followed parameters were the decreasing pain, increasing range of motion (flexion, extension, radial deviation, ulnar deviation, pronation and supination). In the case group it was noticed a significant decrease of pain and an improvement of the usual activities (dressing up, washing, housework, work, recreational activities) and special activities (door knob using affected hand, cut meat using a knife in affected hand, fasten buttons on shirt and push up from chair using affected hand), but not statistically significant difference in wrist motions including radial deviation, ulnar deviation, pronation, supination, flexion, extension in the 3-6 month postoperative period. Research should be extended to larger patient groups and the postoperative follow-up period should be extended to at least 1 year post-injury because some measured parameters of wrist fracture outcome may continue to change up to 1 year post-injury [7].

Recent research demonstrated that the bone regeneration depends on: PRP concentration (a platelet concentration of 1,000.000/µl) that has been linked to positive biological effects in bone regeneration while a medium concentration of PRP (2,65 $x10^9$ml) induced osteogenic differentiation of BMSCs and improved fracture healing, and a high concentration of PRP (8,21$x10^9$ml) inhibited osteogenic differentiation of Bone Marrow derived Mesenchymal stem Cells (BMCs) and delayed callus remodeling; presence or absence of leucocytes (leucocyte-rich PRP induced significantly higher proliferation of BMCs compared to leucocyte-depleted PRP)[8].

Chronic diseases of the hand like osteoarthritis (OA) is characterized by articular cartilage degeneration in the joints and results in pain, swelling, stiffness, muscle atrophy and attendant functional disability [9]. OA can be caused by a single major injury or repetitive small injuries. Radiological progression of disease cannot be prevented by drugs [10]. Existing trials are only few and refer to non-surgical treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) which can be taken orally or applied topically, splint or application of ice did not improve the outcomes, occasionally it can be used steroid injections but their benefit are limited.

Recommendations from American Academy of Orthopedic Surgeons (AAOS) that should be taken into consideration before administering the PRP injection: PRP injection are performed as an outpatient procedure. It can be performed under an

ultrasound guidance to increase precision of the injection in affected area. Corticosteroid drugs must be avoided for 3 weeks before the injection. NSAIDs drugs a week before the procedure are forbidden. Anticoagulation drugs for 5 days before injection are not to be taken.

Conducted trials demonstrated that Leucocyte-poor PRP (P-PRP) is better tolerated in treatment of OA. In the lack of leucocytes that by macrophages and neutrophils maintain inflammation, there have been findings in relieving pain. A total of ten patients with trapeziometacarpal (TMC) osteoarthritis (OA) were treated with 2 intra-articular PRP (P-PRP) injections 4 weeks apart. A volume of 1,5 ml PRP vas injected at each time. Patients with OA were diagnosed using radiographic and clinical criteria: basal joint tenderness, thumb or wrist pain at rest or with activity joint stiffness, decreased mobility, deformity, instability and reduced hand function. No splinting was used after each injection. During the course of treatment, the patients did not take corticosteroids or NSAIDs [11].

Radiological Classification (Eaton and Little) of TMC OA

Stage I: normal joint appearance or less than one third subluxation.

Stage II: decrease of joint space, osteophytes less than 2 mm and one third subluxation or more

Stage III: advanced joint distraction, subchondral cysts and sclerosis, and osteophytes greater than 2 mm.

Stage IV: involvement of several joint surfaces.

All of ten patients were in 3 of 4 stages so 2 patients were in stage II, 3 patients were in stage III and 5 patients were in stage IV. Patients with mild OA (Eaton II) have experienced a significant pain relief between 3 and 6 months follow-up. They had been free of pain after 6 months. Patients classified as Eaton III and IV had pain relief after 3 months which did not fully retain up to 6 months. The grip strength did not improve. Patients in the IV stage of disease experienced a decreased pinch over time [11].

A challenge for modern medicine is to study the possibility of nervous regeneration with PRP after incomplete or complete neurotmesis. Conducted trials on this topic are extremely few at the moment (I have found only 2 to date). Nerve regeneration includes regrowth of injured axons as well as myelination, restoration of synaptic connections and recovery of physiological functions [12].Plasma rich in growth factors (PRGFs) consists a pool of growth factors, microparticles and other bioactive mediators many of them trapped through fibrin heparin sulfate-binding domains in a tridimensional fibrin matrix. Once PRP is infiltrated intraneurally as a liquid-to-gel injectable scaffold or wrapped around the injured nerve gap as a matrix-like viscous and malleable structure, or both, tissue fibrinolysis breaks the fibrin down thereby releasing cell signaling molecules such as neurotrophic. PRP has a therapeutic potential on neural tissue repair and regeneration. These include the prevention of cell apoptosis and neuroprotection, the stimulation of angiogenesis, the modulation of inflammatory microenvironment, the dampening of both denervated muscle atrophy and scarring that follow peripheral nerve trauma and damage [13].

A very interesting case report was described at the beginning of 2018; a 27 years old young patient who suffered a deep and long cut with a knife in the cubital fossa of the right arm, extending proximally towards the radial region with complete neurotmesis of radial nerve. After 48 hours and after the second look of operation an end-to-end suture of the radial nerve was conducted. The skin was closed with metal staples and the member was immobilized with a posterolateral plaster splint. Ten days after surgery the staples were removed, the plaster splint was replaced with a thermoplastic splint in extension in order to begin physiotherapy immediately. Through the rehabilitation program, functional progress was not satisfactory, so an electromyogram (EMG) was required, showing right radial nerve neurotmesis with no tendency to reinnervation. In these circumstances four months after surgery it was performed the first injection with 4ml PRP that was injected into epineurium and also around the injured region. In total five injections were performed, the first three with two-week intervals and the last two with one month interval. Fourteen months after the injury and eleven months after the first PRP injection, functional recovery was achieved. The EMG showed a complete reinnervation of the musculature dependent of the radial nerve [14].

The digital nerves are important in hand function. Affecting them through trauma causes sensory disturbances, hinders delicate movements of the hand such as pinching small objects or hanging buttons [15].

The treatment of digital nerve injury depends of the degree of damage. In case of incomplete

neurotmesis, conservative treatment is chosen because natural recovery can be expected. When we have a complete neurotmesis, epineural suturing under the microscope is performed. Intraoperative local administration of PRP to an injured nerve, promotes functional recovery with no adverse events due to PRP. Studies conducted by the same author have demonstrated that the presence of growth factors in PRP influences the degree of tissue regeneration [16].Another interesting case report belongs to a young female patient who suffered an index finger lesion. She immediately accused sensory disturbances and persistent numbness. She also experienced severe neuropathic pain and anesthesia on her index finger. The patient went to the doctor 2 weeks after the injury. She had a wound scar near the distal interphalangeal (DIP) joint of the ulnar side of the index finger, with hypoesthesia in the thumb, index, middle and little fingers. Severe neuropathic pain was observed both at rest and during movement. The range of motion (ROM) of the index finger was restricted due to neuropathic pain. Neurotmesis was suspected based on clinical findings. After 5 weeks surgical intervention after general anesthesia was performed. Intraoperative findings revealed severe adhesion around the digital nerve, but the nerve preserved its continuity. After neurolysis, 2 x 0,5 ml PRP was intraneurally injected at two locations, from the proximal side of the affected area. After one week of immobilization, rehabilitation of active finger motion was initiated. Neuropathic pain decreased immediately after surgery. Improvement of restricted finger ROM was recognized from two weeks postoperatively, and became normal after four weeks after surgery. Neuropathic pain disappeared after 9 months postoperatively [15].Complete healing in case of traumatic injures depends on the patients age (in both cases they were young), on the complications, duration of denervation, time and size of defect (complete neurotmesis of radial nerve, total rehabilitation period, after 5 injection and 14 months, incomplete neurotmesis of digital nerve, 1 injection and 6 months). However, PRP injection has been shown to help reduce neuropathic pain and speed recovery in both cases.

Neuropathic chronic disease in wrist and hand are more widely known in the literature because there are several studies on the effects of PRP in carpal tunnel syndrome (CTS). All the patients with carpal tunnel syndrome, included in these trials suffered from mild to moderate pain. 14 of them had obvious symptoms for over 3 month. They received a single dose of 1-2 ml of PRP which was injected under ultrasound guidance around the median nerve at the proximal edge of the carpal tunnel. 8 patients from 14 had full recovery, without pain, 3 patients with alleviate pain and the last 3 still experienced pain. At 3 months follow-up period, poor or fair improvement was found in 3 patients and one open surgery for carpal tunnel syndrome was performed. The study showed encouraging short period results [17].A group of 60 patients with mild to moderate CTS were randomized into two groups of 30, the PRP group or the case group and the control group. In the case group patients were injected with a single dose of 3 ml PRP using ultrasound guidance. The control group received night splint through the study period. The evaluation was performed before treatment and at 1, at 3 and 6 months post injection. The patients from case group experienced a significant pain relief, ameliorated disability and improved cross-section of median nerve at 6 months post-treatment [18].

A total of 41 women with mild to moderate CTS symptoms were included in two groups. 20 wrists as control group and 21 wrists as PRP group. The patients of control group received a wrist splint at 5 degree wrist extension and were instructed to put the splint overnight for 8 weeks. Subjects of PRP group also received wrist splints and were instructed to use it similar to the control group. They were also treated with a single local injection of leucocyte-poor PRP (P-PRP).One ml P-PRP was injected to the patients of PRP group. The follow-up period was 10 weeks for both groups. A single dose of PRP injected in the wrist did not add significantly to the benefit of wrist splinting at 10 weeks follow-up [19].

Results and Discussions

Of all patients with bone disease (40), 75% have experienced acute lesions (intra-articular distal radius fracture) and 25% chronic disease (OA). Operated patients who received a single dose of PRP experienced a significant decrease of pain and improvement of the usual activities and special activities but only for a short period, which means that a first bone regeneration process was started (initiated), maybe the follow-up period should be extended to at least 1 year and the number of PRP injections should be supplemented. Also in patients with bone trauma and without associated

comorbidities it would be worth trying the PRP options (L-PRP and L-PRF) besides a good knowledge of cell engineering. Provided that of knee OA there have been several conducted trials, about the other joint's OA and especially of those of wrist and hand OA, there haven't been many publications. The studies outcomes have shown that intra-articular injection with PRP in TMC OA is a safe, conservative method for a short period. Patients with mild to moderate form of TMC OA have experienced a decrease in pain even after 6 months post injection with two doses of PRP. In traumatic lesion all types of PRP could be tried out, while in chronic diseases administration of L-PRP and L-PRF is in question based on the chronic inflammation in the joint. Therefore the used alternative is the poor version with reduced cellularity and obviously with smaller benefits. Also the long term effect of joints in chronic diseases with bone destruction are aggravating a lot the regeneration process. The most obvious progress in posttraumatic and postoperative rehabilitation after epineural injection of PRP was observed in peripheral nerve lesions (trauma). Although it required a longer period of rehabilitation (9 to 14 months respectively), the recovery was full. We must admit that due to the fact that there are only two cases, the obtained outcomes are not conclusive, but the achieved progress motivates us for further research. In case of chronical disease of median nerve (carpal tunnel syndrome), of 115 patients with mild to moderate pain, 65 meaning 56,52 % received a single dose of PRP, while the other 50, meaning 43,47% did not receive at all. Patients from the case group (PRP group) have shown a decrease in pain and an improvement in hand functionality compared to the control group which has benefited of night splinting immobilization.

In the group with the patients with night splint, the difference between those who received a single dose of PRP and those who didn't was not significant.

Conclusions

1. The medical literature contains few publications regarding the efficiency of PRP in treatment of traumatic lesions and chronic disease of forearm, wrist and hand.

2. In chronic condition the favorable outcomes after the PRP injection are obtained only in the first stage of the disease, in advanced stages the surgical treatment is mandatory.

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