Review Article

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The effect of platelet rich plasma on radiotherapy

Trombositten zengin plazmanın radyoterapide etkisi

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Abstract: The basic principle in the clinical use of Platelet Rich Plasma (PRP) is to increase the innate repairability of the human body and accelerate recovery after injury. PRP, a source of natural growth factors, emerges as a treatment method to reduce the side effects related to radiotherapy. PRP exerts its radioprotector effect by stimulating angiogenesis, epithelialization, cell differentiation and extracellular matrix formation in aged and poorly regenerated tissues. Additional studies are needed to confirm the promising effect of PRP in beam therapy.

Keywords: platelet rich plasma; radiotherapy.

Özet: Trombositten zengin plazmanın (TZP) klinik kullanımındaki temel prensip insan vücudunun doğuştan gelen tamir yeteneğini arttırmak, yaralanma sonrası iyileşmeyi hızlandırmaktır. Doğal büyüme faktörleri kaynağı olan TZP radyoterapiye bağlı yan etkileri azaltmak için bir tedavi yöntemi olarak ortaya çıkmaktadır. TZP radyoprotektör etkisini yaşlı ve rejenerasyonu iyi olmayan dokularda anjiyonegenezi, epitelizasyonu, hücre farklılaşmasını ve ekstraselüler matriks formasyonunu stimüle ederek göstermektedir. Işın tedavisinde TZP'nin umut verici etkisini doğrulamak için ek çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: radyoterapi; trombositten zengin plazma.

Introduction

Platelet Rich Plasma (PRP) is an autologous blood product obtained by the centrifugation of venous blood from the patient, containing 3 to 5 times the density of basal plasma. It is one of the regenerative treatments such as stem cell, prolotherapy, extracorporeal shock wave, sclerosing agents, nitric oxide. The aim is to activate the body's repair mechanisms. Depending on whether the PRP is autologous, it is an atoxic, organic, non-immune reactive product and there is no risk of infection. Depending on the characteristics of the target tissue, it can be used intra-operatively, injection or topically. It is not used in patients with critical thrombocytopenia, hypofibrinogenemia, sepsis, anemia, pregnancy, breastfeeding, tumor presence and metastatic disease, acute and chronic infections [1–7].

There is no standard practice accepted in PRP preparation and clinical application. There are many different protocols and platelets can be obtained in different concentrations [8–15]. Differences between the protocol and devices used; blood volume (9–120 mL), PRP volume (3–32 mL), activators used (CaCl₂, thrombin, batroxobin), centrifuge number (1 or 2 times) affect the platelet concentration to be obtained [10, 11, 13]. There are three methods to prepare PRP: (1). Double-dial method using automated machines with commercial kits; it contains high platelet concentration (up to 8 times) and a high amount of leukocytes [13]. (2). The single-dial method using traditional laboratory methods, where blood is centrifuged and manual PRP is separated; Contains platelet concentration up to 3 times the poor basal level from white blood cell, low cost [11]. (3). The method of filtering blood using commercial technological means; it contains a low number of leukocytes, high platelets and PDGF concentrations, but is high cost. When using the double-turn method, 10% of the blood collected from the patient is obtained, while a greater amount of whole blood is required for the same amount of platelet in the single-

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turn method. However, during the preparation of PRP, platelet disintegration should be prevented during centrifugation and the integrity of the platelet membrane should be preserved. Otherwise, platelets activate secreted growth factors and a biologically inactive PRP is obtained [14].

PRP component

The main cellular component of PRP are platelets and white blood cells. The cellular component of the plasma normally consists of 93% erythrocytes, 6% platelets and 1% leukocytes. In PRP, this rate is 93% platelets, 6% erythrocytes and 1% leukocytes. With the activation of platelets, many molecules are known as coagulation factors, growth factors (PDGF-AA, PDGF-BB, PDGF-AB, TGF- β 1, TGF- β 2, VEGF, EGF), cytokines, chemokines and integrins are released [2, 3, 6, 8, 16, 17] According to the full blood in PRP in the analysis; It was shown that TGF- β levels were 7 times, PDGF levels were 30 times and EGF levels were 10 times higher. These biological growth factors stimulate the profile and differentiation of fibroblasts, osteoblasts, chondrocytes and mesenchymal stem cells. Although it has been suggested that the growth factors contained in the theoretical content of PRP may have a cancer-like effect due to its effects on increasing cell proliferation, no information supporting this hypothesis has yet been reported. The growth factors found here are not mutagenic because they are proteins that act on the cytoplasmic membrane, not on the cell nucleus. Platelets continue to secrete and synthesize additional growth factors for the remaining 7–10 days of life after secreting the initial growth factors. These substances released from platelets play a role in many pathophysiological mechanisms, including hemostasis and thrombosis, tissue repair, cellular chemotaxis, extracellular matrix formation, vascular contraction and repair, atherosclerosis, autocrine and paracrine activation, inflammation, immune system and even tumor growth / metastasis [8–12].

PRP usage area

PRP was used for the first time in 1987 in an open heart operation. It was then used in the dental health field to accelerate healing after jaw reconstruction in cancer patients, improve bone healing after spinal cord injury, and support soft tissue repair. It gained widespread popularity in 2009. PRP is used in different fields due to all these mechanisms of action and not being immunogenic.

Tendinopathies in physical therapy; bone, cartilage and tissue defect repair in orthopedics; alopecia in dermatology; It is applied in many areas such as burn and ulcer treatment in plastic surgery [1, 2, 3, 7, 9–12]. Hegab et al. reported that PRP improves symptoms and function in temporomandibular joint osteoarthritis [11]. Filardo et al. applied PRP with intraarticular injection every three weeks and 3 times in patients with knee joint osteoarthritis. Patients were checked at the 6th, 12th and 24th months after the last injection. The study stated that while some patients did not improve, some patients continued to recover after 24 months and there was no deterioration. The average duration of action of PRP has been specified as nine months [10]. Poeschl et al. used PRP combined with graft material in sinus augmentation and evaluated its effect on bone healing. As a result of the study, they found more graft resorption and new bone formation in the group where PRP was applied [9]. Robiony et al. stated that PRP increases the rate of bone formation in patients with atrophic mandible with bone graft. They reported that this was achieved through growth factors such as PDGF and TGF- β released from activated platelets in the PRP [12]. In the study of Jackson, PRP was injected under the flap after abdominoplasty. With this application, it has been reported that better quality and faster wound healing are obtained in addition to the marked decrease in the formation of seroma [7]. Del Rossi et al. reported that with autologous PRP infusion after cardio-pulmonary bypass surgery, easier bleeding control and improvement in hematological parameters can be achieved in the post-operative period [16]. Studies have reported that the patient's age, gender, race, skin quality, concomitant diseases, initial wound site, wound depth, wound time, wound localization, the platelet count in the PRP change the PRP application results [4].

PRP in radiotherapy

There are very few studies on the effect of PRP on the treatment of cancer patients. Studies report that PRP injections are also very useful in cancer treatment with radiotherapy. There are also authors who argue that its effect is not superior to placebo. The reason for this is generally explained by the differences in the preparation of PRP. Studies are usually on cell culture or animal experiments, and the number of clinical trials is very limited. They looked at the effect and reliability of PRP in chronic wounds caused by radiation from Reinders et al. They reported that PRP shows proliferation on fibroblasts and endothelial cells in irradiated cell cultures, while it has the

opposite effect on keratinocytes. As a result, it has been stated that PRP therapy may be beneficial in radiation-induced chronic wounds [17]. In phase 1 study on rats, it was stated that PRP is protective against nephrotoxicity that may occur due to radiation by improving oxidative stress due to gamma radiation and inhibiting induced apoptosis [18]. In another similar study, it was reported that PRP prevents ERK and Akt signaling pathways and prevents radiation-induced hepatotoxicity [19]. In a study conducted by Elsaadany et al. in rats, PRP reported that radiation has a positive effect on wound healing by decreasing apoptotic activity in oral mucosal damage [20]. In another experimental study, it was stated that PRP applied in the temporomandibular joint, which may be due to radiotherapy and to prevent and/or treat late complications, causes increased blood flow and regeneration. It has been reported that it can minimize side effects such as the painful jaw, malnutrition and weight loss [21]. In studies conducted by Reinders et al., PRP has been reported to have a protective effect on external radiotherapy [17, 22]. In studies on cell culture, PRP has been shown to affect chronic wound healing caused by radiation by increasing the basic fibroblast growth factor [23]. As seen in all these Phase 1 studies, PRP appears to reduce the side effects associated with radiotherapy.

Positive results of studies on cancer treatment are reported when PRP is used with radiotherapy or used alone. However, these studies are limited. Barbieri et al. looked at PRP's effects on tumor recurrence using the mouse model in human fibrosarcoma. In the PRP-treated group, lesion recurrence and tumor growth decreased (without statistical significance; $p=0.12$). They reported that PRP slowed tumor growth as well as stimulating tissue repair and accelerating healing [3]. In the study of Omar et al. in rats, they evaluated the PRP in the prevention of radiation-induced malignancies. It has been reported that PRP can decrease tumor development by suppressing inflammation, induction of M2 macrophage phenotype, ActR-IIA/FST signaling downregulation [24]. In another study conducted in rabbits, they looked at PRP's effect in adjuvant treatment in the group that received dental implants in the tibia and then received the group with radiotherapy. As a result, they reported that PRP had an effect by increasing the osseointegration process [25].

In the literature, there are very few phase 2 studies and reviews that indicate the place and importance of PRP in radiotherapy. In the review written by El-Rabbany et al. it was emphasized that PRP applied to curative or adjuvant radiotherapy did not have an effect on prophylaxis in preventing osteoradionecrosis in the chin [26]. In a randomized, double-blind controlled study planned by

Batstone et al., they looked at the efficacy and safety of PRP in patients requiring pre-treatment tooth extraction for patients receiving radiotherapy to the mandible. Patients were followed for five years. After treatment, 22 patients developed within one year, and three patients developed within five years. They stated that PRP has no benefit in preventing osteoradionecrosis, pain scores or mucosal healing [27]. In a retrospective study, PRP's effectiveness was investigated in patients who were operated due to squamous cell carcinoma and applied radiotherapy. PRP was applied to the area where the graft was applied before and after radiotherapy in high doses. They stated that PRP accelerated wound healing. They reported this by increasing the multiplication of osteoblasts and antimicrobial effects in the lower part of the graft [28].

Conclusion

The basic principle in the clinical use of PRP is to increase the innate reparability of the human body and accelerate recovery after injury. PRP, a source of natural growth factors, emerges as a treatment method to reduce the side effects related to radiotherapy. PRP exerts its radioprotector effect by stimulating angiogenesis, epithelialization, cell differentiation and extracellular matrix formation in aged and poorly regenerated tissues. Additional studies are needed to confirm the promising effect of PRP in beam therapy.

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