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A systematic review of the safety and efficacy of platelet-rich plasma for the treatment of posttraumatic knee osteoarthritis

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ABSTRACT

Injury of the knee joint can lead to a range of adverse outcomes and significantly contributes to the development of the knee osteoarthritis. Currently, autologous platelet-rich plasma is used as a promising and safe method of treating osteoarthritis. Such plasma contains various growth factors, some of which are secreted after platelet activation. These factors can trigger a regenerative response and improve the metabolic functions of damaged structures. However, there are different protocols for preparing platelet-rich plasma, which results in preparations with different amounts of bioactive substances. As a result, the data obtained on the effect of platelet-rich plasma on the restoration of hyaline cartilage of the knee joint are very contradictory. A search for publications on a given topic was performed in the eLibrary, PubMed (MEDLINE), Ovid, Science Direct, Google Scholar databases, and also a search was conducted for clinical trial data on the treatment of knee osteoarthritis with platelet-rich plasma over the past 20 years. Publications dealing with other aspects of the application of this technology were excluded from the search results. An analysis of published clinical trial results found that, in most cases, patients treated with platelet-rich plasma reported improved pain and joint function, with only three studies showing no difference between platelet-rich plasma and placebo. Thus, this technology is generally promising for use in the treatment of knee osteoarthritis, however, methods of obtaining and activating platelet-rich plasma, as well as the age and comorbidities of the patient, may affect the effectiveness of therapy.

Keywords: hyaline cartilage; chondrocytes; VEGF; platelet rich plasma; review.

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Систематический обзор безопасности и эффективности применения обогащённой тромбоцитами плазмы для лечения посттравматического остеоартрита коленного сустава

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АННОТАЦИЯ

Травма коленного сустава может привести к целому ряду неблагоприятных последствий и в значительной степени способствует преждевременному развитию остеоартрита коленного сустава. В настоящее время в качестве перспективного и безопасного метода терапии остеоартрита используют аутологичную обогащённую тромбоцитами плазму. Такая плазма содержит различные факторы роста, часть которых секретируется после активации тромбоцитов. Эти факторы могут запускать регенеративный ответ и улучшать метаболические функции повреждённых структур. Однако существуют различные протоколы приготовления обогащённой тромбоцитами плазмы, что приводит к получению препаратов с разным количеством биоактивных веществ. В результате полученные данные о влиянии обогащённой тромбоцитами плазмы на восстановление гиалинового хряща коленного сустава весьма противоречивы. Поиск публикаций по заданной теме был выполнен в базах данных eLibrary, PubMed (MEDLINE), Ovid, Science Direct, Google Scholar, а также был проведён поиск данных клинических испытаний по терапии остеоартрита коленного сустава с помощью обогащённой тромбоцитами плазмы за последние 20 лет. Публикации, посвящённые другим аспектам применения этой технологии, были исключены из результатов поиска. Анализ опубликованных результатов клинических испытаний показал, что в большинстве случаев пациенты, которым вводили обогащённую тромбоцитами плазму, сообщали об уменьшении болевых ощущений и восстановлении функции сустава, и только три исследования не выявили разницы между введением обогащённой тромбоцитами плазмы и плацебо. Таким образом, эта технология в целом перспективна для применения в терапии остеоартрита коленного сустава, однако методы получения и активации обогащённой тромбоцитами плазмы, а также возраст и сопутствующие заболевания пациента могут оказывать влияние на эффективность терапии.

Ключевые слова: гиалиновый хрящ; хондроциты; VEGF; обогащённая тромбоцитами плазма; обзор.

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INTRODUCTION

Traumatic knee injury is common in young people and contributes significantly to the development of knee osteoarthritis (OA). The risk of OA increases with the age of the patient at the time of the injury and with the time from the injury [1]. Patients with cartilage injury are at high risk of developing post-traumatic OA [2]. About 1.5 million cases of knee injuries are registered annually in Russia, most of them can give rise to the development of post-traumatic OA.

Post-traumatic OA is an abnormal remodeling of joint tissues and is based on an inflammatory process [3], which, according to many authors, plays a crucial role in the development of a chronic disease. A number of inflammatory mediators are released into the synovial fluid immediately after joint injury. These molecules have been proposed as disease markers and potential targets for the development of specific preventive interventions [1].

There is a wide range of methods for local restoration of the hyaline cartilage surface of the knee joint (microfracturing using biodegradable scaffolds, autologous chondroplasty, and many others) which are constantly being modified in order to increase restoration efficiency [4, 5]. Cell-based implantation therapy uses either autologous chondrocyes [6, 7] and mesenchymal stromal cells [8] or allogeneic cell products [9, 10].

The latter is possible due to immune tolerance of hyaline cartilage. The combination of cells with a scaffold made from fibrin [11], esterified hyaluronic acid [12] or allogeneic cartilage [13] improved the biomechanical properties of the implant, allowing the better regeneration. Despite the successful application of the above approaches to therapy, the final stage of treatment still remains an operation to replace the knee joint with an artificial endoprosthesis. This intervention is a costly, high-risk and highly invasive procedure.

One of the promising approaches to prevent the development of chronic OA is the use of platelet rich plasma (PRP) obtained from the patient's own blood or commercially available PRP [14]. Despite the fact that PRP therapy is actively used in clinical practice for the treatment of knee OA, at present the evidence base for its effectiveness remains limited [15, 16]. We have found 59 completed clinical trials (search was done on ww.ClinicalTrials.gov with word combination PRP and knee osteoarthritis), only 33 of them have published results. In 27 studies the positive effect of PRP treatment on reducing pain and symptoms and recovering articular function was observed, and only in 3 cases PRP treatment was not superior to placebo. PRP showed a better performance in younger patients affected by OA on early stages. Different methods of PRP preparation and activation, patient age, and comorbidities make it difficult to compare or reproduce results. The functional properties of PRP are mainly based on the activity of multiple growth factors secreted after platelet activation. Many growth factors also show a synergistic effect on chondrogenesis by activating various intracellular signaling pathways and enhancing tissue regeneration [17].

At the same time, high concentrations of some growth factors may have an opposite effect on cartilage regeneration. For example, VEGF, a vascular endothelial growth factor present in PRP, stimulates the growth of new vessels, attracts immune cells, and may contribute to the development of chronic osteoarthritis at certain stages of the disease [18].

The purpose of this review is to evaluate the safety and efficacy of platelet-rich plasma (PRP) for the treatment of post-traumatic knee osteoarthritis based on the analysis of scientific literature and published clinical trials. Taking into regards the variation of PRP composition and age of the patients one can assume that this treatment might be more effective in younger patients with initially high platelet count.

HYALINE CARTILAGE

Hyaline cartilage is a highly specialized connective tissue consisting of a large amount of water and extracellular matrix components with a small (no more than 5%) content of highly specialized cells — chondrocytes. Hyaline cartilage lacks nerve endings, blood vessels, and lymphatic vessels, so metabolism occurs primarily by diffusion into and out of adjacent tissues. The specificity of the structure of hyaline cartilage allows it to ensure the joint function with minimal friction and withstand significant reversible mechanical loads. However, this also limits its regenerative capabilities, and even after minor damage, the articular cartilage cannot fully recover and continues to break down further. The hyaline cartilage matrix consists of type II collagen and various combinations of proteoglycans and glycosaminoglycans synthesized by chondrocytes. Cartilage lacks calcium and contains a large amount of chondroitin, a material that provides elasticity and flexibility [19].

During calcification, cartilage is replaced by bone tissue, which leads to the death of chondrocytes. It is assumed that the lack of active blood flow is the main reason of the time-consuming healing of any cartilage injury. The use of platelet-rich plasma to stimulate the regeneration of damaged cartilage may be a promising therapeutic strategy.

THERAPEUTIC EFFECT OF PRP

PRP therapy is currently considered as an effective treatment for many diseases of the musculoskeletal system, but it remains a widely discussed topic in regenerative medicine [20]. In orthopedics, PRP technology consists in the intra-articular injection of an autologous plasma preparation with a platelet concentration that is 3–5 times higher than the physiological concentration of platelets in the whole blood of a healthy person. PRP preparations are obtained from the patient's blood by sequential centrifugation according to a special protocol [21].

However, protocols for preparing and activating PRP vary among manufacturers, and thus the resulting products differ both in platelet concentration and in the presence and

concentration of various biologically active molecules. The composition of PRP may also depend on the age of the patient, gender and the presence of certain diseases [22]. The resulting PRP product can be addressed as pure PRP, Red-PRP, L-PRP or Red-L-PRP based on final platelet amount and presence/absence of red blood cells and white blood cells (presented on Fig. 1).

Platelets are formed in the bone marrow from megakaryocytes and in a healthy person their number normally ranges from 150,000/μl to 450,000/μl [23]. Platelet activation due to vascular injury leads to the release of granules loaded with growth factors, which ultimately stimulates the inflammatory cascade and the tissue healing process [24]. The cellular response to tissue damage goes through four main stages: hemostasis, inflammation, proliferation, and synthesis of extracellular matrix components. Blood plasma and platelets are responsible for hemostasis, while leukocytes and activated platelets mediate inflammation, and growth factors derived from platelet α-granules affect tissue regeneration [25].

Accordingly, the therapeutic effect of PRP is based on the activity of various growth factors released from platelet alpha granules (presented on Fig. 2). These factors stimulate cartilage matrix synthesis and counteract the action of catabolic cytokines such as interleukin-1 and tumor necrosis factor-α (TNF-α). The main PRP growth factors include transforming growth factor beta (TGF-β), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF) and fibroblast growth factor (FGF) [26, 27].

A number of growth factors, when combined with TGF-β, have been found to have a synergistic effect on cartilage matrix synthesis. However, a high concentration of VEGF can backfire and cause further cartilage degradation. It is believed that VEGF is one of the most important factors that can cause the development of arthritis [28]. In this regard, the removal of VEGF from PRP using antibodies bevacizumab [29] or a soluble form of the sFlt-1VEGF receptor capable of efficiently binding VEGF *in vitro* [30, 31] increases the effectiveness of PRP in the treatment of cartilage damage.

Another approach to optimize PRP composition could be the addition of hyaluronic acid (HA) [32]. HA is an important component of the extracellular matrix, belongs to non-sulfated glycosaminoglycans [33, 34]. Its negative charge is formed by carboxyl groups, which provide hydrophilic properties. When hyaluronic acid binds to aggrecan monomers, large negatively charged aggregates that absorb water are formed in the cartilage. These aggregates are responsible for cartilage elasticity [33].

Intra-articular injections of hyaluronic acid are used to treat symptomatic knee osteoarthritis. Preclinical studies in rats with experimental osteoarthritis showed a higher efficacy of therapy with intra-articular injection of PRP + HA, compared with the introduction of HA alone [35]. A number of randomized controlled clinical trials have demonstrated

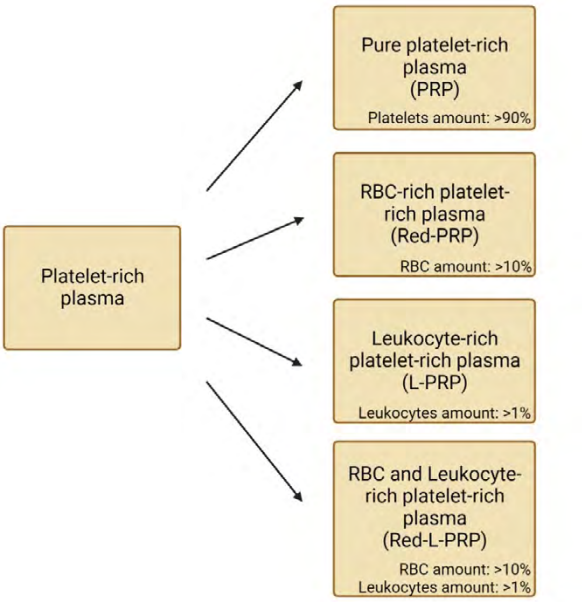

Fig. 1. Classification for platelet-rich plasma preparation; PRP — platelet-rich plasma; RBC — red blood cells

that the results of the PRP injection directly into the knee joint cavity are superior to the effect of similar injections using HA [36, 37].

Benefits of PRP over HA administration have been observed in the treatment of mild to moderate knee osteoarthritis in young and male patients [38]. A meta-analysis conducted by Chinese scientists found that combination therapy with PRP + HA did not outperform knee osteoarthritis with PRP alone. However, based on meta-analysis data, the authors recommend the use of combined PRP + HA preparation, as this procedure is generally safer than PRP injections alone when assessing the incidence of side effects. However, the heterogeneity of data acquisition used for meta-analysis should be noted. The age of patients was highly variable (from 40 to 60 years); follow-up time was limited (up to 6 months); the PRP composition was not standartized; so it is impossible to assess the long-term efficacy and safety of PRP + HA therapy [39].

A meta-analysis conducted by American scientists showed that despite minor improvements after using PRP in the treatment of knee osteoarthritis after 6 months, there was no significant improvement in the long term. The age of the patients ranged from 53 to 66 years. The authors of the meta-analysis emphasized that the effectiveness of the application and assessment of changes in the structure of the knee joint after the introduction of PRP, despite the rapid increase in the use of PRP in orthopedic clinics, is uncertain [16]. Moreover, the administration of hyaluronic acid is not suitable for all patients with knee osteoarthritis, as it can cause side effects such as increased pressure, proteinuria, swelling at the injection site [40, 41].

Italian scientists have shown the effectiveness of PRP in older patients (from 40 to 65 years) only in the initial stages

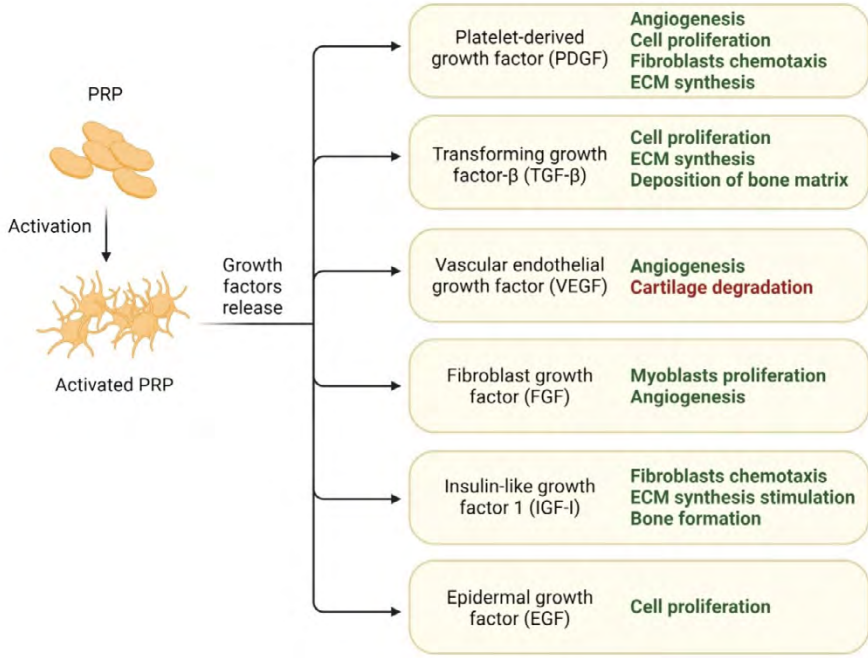

Fig. 2. Main growth factors released from platelet alpha granules; PRP — platelet-rich plasma; ECM — extracellular matrix

of osteoarthritis and with repeated administration of PRP [42]. From this we can conclude that the intra-articular injection of hyaluronic acid is recommended only for patients with a mild form of the disease, in which conservative treatment has been ineffective. In severe OA of the knee joint, the effect of HA on healing is markedly reduced [43]. In the elderly, the combined use of hyaluronic acid (HA) with PRP also does not have a clinically significant effect [44]. On the other hand, studies conducted on athletes after a knee injury (age less than 50 years) with a three-time injection of the PRP preparation demonstrated a high effectiveness of treatment. About 50% of patients after treatment were able to return to their previous activity [45].

GENERAL PRINCIPLE OF PRP PREPARATION

Receiving autologous PRP from the patient's blood is carried out in several stages (presented on Fig. 3).

1. First centrifugation: The patient's venous blood is mixed with an anticoagulant, or left intact [46] and centrifuged to separate red blood cells from plasma. There are various protocols for centrifugation speed, time and temperature. The recommended settings for the first centrifugation are 100–300 G for 5–10 minutes.

2. Fractionation: Collect the upper fraction of the supernatant to obtain pure PRP (P-PRP), which contains predominantly platelets. To obtain leukocyte-enriched L-PRP, the upper and middle fractions of the supernatant are collected.

3. Second centrifugation: The obtained supernatant is centrifuged at higher speeds than in the first stage, and then most of the supernatant is removed. There are various protocols for centrifugation speed, time and temperature. The recommended settings for the second centrifugation are 400–700 G for 10–17 minutes

4. Resuspension: The pellet containing platelets is resuspended in a small volume of remaining plasma (1/5–1/6 of the original volume).

5. Activation: Platelets are activated to release growth factors from the cytoplasmic granules. This is achieved by exposing platelets to thrombin or calcium chloride.

The recommended concentration of platelets in PRP is 1–1.5 million platelets/μl [47]. It must be taken into account that variations in the speed, duration and temperature of centrifugation can change the concentration of platelets in the final PRP product [48, 49]. In addition, the initial concentration of platelets in the patient's blood also greatly influences their final concentration.

PRP ACTIVATION METHODS

PRP activation is an important step leading to the release of growth factors from platelet granules into the external environment. The term “activation” refers to two key processes initiated during PRP preparation: (1) platelet degranulation to release GF from alpha granules, and (2) fibrinogen cleavage to initiate the formation of a matrix that forms a gel around the platelets and spatially restricts the secretion of molecules [50].

There are several methods for activating PRP, for example, adding 10% $CaCl_2$ (final concentration 22.8 mM), 10% autologous thrombin (final concentration 1 U/ml), 10% $CaCl_2$ +

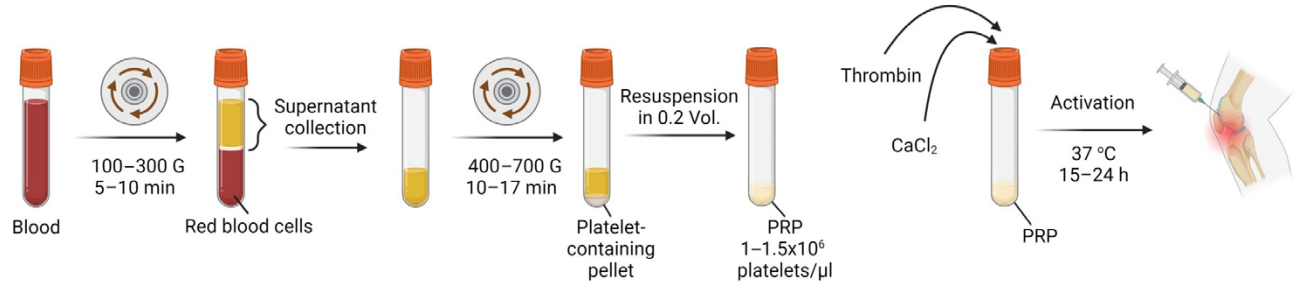

Fig. 3. Stages of platelet-rich plasma preparation; PRP — platelet-rich plasma

thrombin, 10% type I collagen (final concentration 4 µg/ml). Next, PRP is incubated at 37 °C (from 15 to 24 hours) and centrifuged at 2800×g for 15 minutes at 20 °C. The resulting samples are stored at –80 °C until use [50].

Thrombin is a serine protease that plays a critical role in platelet aggregation and activation and blood clotting. It is formed from prothrombin after tissue damage and cleaves fibrinogen to fibrin at the final stage of the blood coagulation cascade [51]. Thrombin also activates factor XIII, causing fibrin monomers to cross-link, resulting in the formation of a dense fibrin clot. Classical protocols used bovine thrombin to activate PRP, resulting in allergic reactions [52]. Therefore, in modern protocols, they switched to the use of autologous thrombin obtained from the patient's whole blood [53].

Activation with calcium chloride results in the formation of less dense clots compared to activation with thrombin. The addition of a small amount of $CaCl_2$ reduces the burning/tingling sensation experienced by some patients during PRP injections. The combination of $CaCl_2$ and thrombin creates a dense fibrin-platelet matrix. The resulting matrix can be used in surgical operations to accelerate the healing of postoperative wounds. Platelets within the matrix undergo degranulation and release of growth factors that promote tissue regeneration and healing [54].

The use of thrombin to activate PRP also stimulates the release of endostatin through its interaction with the thrombin receptor PAR4 (proteinase-activated receptor-4). The use of a specific PAR4 peptide agonist (AYPGKF-NH2; AY-NH2) had a positive effect on the release of endostatin [55]. On the contrary, activation of the thrombin receptor PAR1 led to preferential release of VEGF, and the use of the non-peptide PAR1 antagonist SCH79797 reduced the release of VEGF and stimulated the release of endostatin [56].

The principal role of endostatin in the process of chondrogenic differentiation was shown, in particular, in experiments on a culture of neonatal porcine meniscus cells. The use of exogenous endostatin stimulated the synthesis of type I and II collagen and SOX9 protein, an early marker of chondrodifferentiation [57].

Many clinicians choose not to activate PRP *in vitro*, but inject it directly into damaged tissue, where it is activated upon contact with collagen. This method of activation *in vivo* leads to a slower but prolonged release of growth factors compared to the thrombin method [58]. Specifically, collagen activation results in a longer TGF-B1 release and an 80% increase in cumulative release over a 7-day period compared to thrombin activation [58].

An additional advantage of *in vivo* activation is that PRP can then be administered through a smaller gauge needle as no coagulated gel is formed. To date, there is no consensus on the frequency and volume of injected plasma, however, European experts recommend 1–3 injections of 4–8 ml of PRP per course of treatment [59]. In recent studies, a positive effect was shown for 2, 3 and 4 injections [52, 60].

CONCLUSION

Many basic scientific data support the therapeutic potential of PRP. Over the past decade, the frequency of PRP use has increased significantly, in total more than half of the studies showed a positive effect of such therapy, however, the methods of preparation and activation of PRP, as well as the age and comorbidities of patients, could influence the results. PRP preparation protocols vary widely among authors, making it difficult to compare or reproduce results. It is recommended to conduct 2–3 intra-articular injections of PRP with a platelet concentration of at least 1 million/µl for patients under 44 years with minor joint damage and the initial stage of osteoarthritis. It should be noted that there are no detailed open source reports of PRP clinical trials.

Therefore, further well-designed and standardized studies are needed to evaluate the effectiveness of PRP therapy and the transition to individualized treatment. Thus, the use of PRP therapy is a promising technology for repairing defects in the surface of the hyaline cartilage of the knee joint.

However, methods of obtaining and activating PRP, as well as the age and comorbidities of the patient, can affect the effectiveness of therapy. For the introduction of PRP-therapy into extensive clinical practice and the transition to individual treatment, additional experimental and clinical studies are required to increase the effectiveness of its use by modifying the composition and regulating the concentration of its individual components.

ADDITIONAL INFORMATION

Authors' contribution. E.I.L. — conceptualization, writing — original draft, supervision, writing — review & editing, funding acquisition; Ju.V.S. — writing — review & editing, project administration; A.V.Ch. — visualization, writing — review & editing. Pictures were created in the BioRender program.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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