doi: 10.21823/2311-2905-2019-25-3-57-66

PRP-Therapy for Tendinopathies of Rotator Cuff and Long Head of Biceps

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Abstract

Relevance. Owing to its controlling action on the inflammatory process, pain-relieving and reparative effects the RPR-therapy became quite demanded for treatment of certain types of tendinopathies specified by prevalence of degenerative process and poor reparative potential. ***Purpose of the study*** — to evaluate the efficiency of PRP-therapy in patients with tendinopathies of rotator cuff (RC) long head of biceps (LHB) tendons. ***Material and Methods.*** The paper presents the results of two-center prospective study for application of autologous platelet rich plasma in treatment of 122 patients: 53 men and 69 women aging 46.8±6.8 years who suffered RC tendinopathy (66%), subacromial impingement syndrome and RC tendinopathy (17%) and LHB tendinopathy (17%). Treatment outcomes were evaluated in 1, 3 and 6 months after PRP-therapy using various scales — VAS, UCLA, DASH, — and instrumental examination methods (US, MRI). ***Results.*** The authors observed statistically significant improvement in pain and functional scores in all three groups as compared to reported scores prior to PRP-therapy during 6 months follow up. During this period of evaluation, the scores of UCLA and DASH in patients with RC tendinopathy improved at 8.6 and 36.4 points, with subacromial impingement syndrome and RC tendinopathy — at 9.6 and 38.8 points, with LHB tendinopathy — at 11.5 and 44.1 point, respectively. The most notable reduction of pain syndrome by VAS was achieved in treatment of LHB tendinopathy (at 5.4 points) and RC tendinopathy (at 5.2 point). The highest average scores of satisfaction with treatment outcomes were reported in patients with RC tendinopathy (2.3) and LHB tendinopathy (2.2). MRI and ultrasound examinations after PRP-therapy demonstrated improved structure of RC and LHB tendons — decreased or eliminated swelling, areas of hypoechoic signal. ***Conclusion.*** PRP-therapy in patients with RC and LHB tendons and with subacromial impingement syndrome with RC tendinopathy significantly reduces severity of pain and improved the shoulder joint function with positive dynamics during 6 months follow up.

Keywords: platelet rich plasma, tendinopathy, rotator cuff, long head of biceps.

Cite as: Malanin D.A., Norkin A.I., Tregubov A.S., Demeshchenko M.V., Cherezov L.L. [PRP-Therapy for Tendinopathies of Rotator Cuff and Long Head of Biceps]. *Travmatologiya i ortopediya Rossii* [Traumatology and Orthopedics of Russia]. 2019;25(3):57-66. (In Russian). doi: 10.21823/2311-2905-2019-25-3-57-66.

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Received: 21.03.2019. Accepted for publication: 10.07.2019.

Introduction

The term "tendinopathy" determines a quite wide range of clinical conditions of different localizations, today. In recent years, the inflammatory nature of the tendinopathies was subjected to reasonable doubt. New theories suggest that the traditional explanation of etiological factors and pathophysiological mechanisms only from the point of view of inflammation does not always reflect the true state of affairs, and the processes, which occur during the tendinopathies, have a more complicated level of interaction [1].

The tendinopathies in the shoulder joint are observed in 15-20% of people engaged in physical labor [2]. Moreover, a subacromial impingement syndrome, which occurs in 18% of the athletes whose physical activity is associated with loads on the upper shoulder girdle, is considered a potential cause of tendinopathy of the rotator cuff. Due to the close anatomical and functional relationship, tendinopathy of the tendon of the biceps is observed in 41% of cases of diseases of the rotator cuff of the shoulder, which is also often associated with impingement syndrome [4].

The etiology of the tendinopathies remains not entirely clear, and the most of the known causes, such as hypoxia, hyperthermia, apoptosis, exposure of the inflammatory mediators, of the lactic acid ("oxidative stress"), imbalance of matrix metalloproteinases and others, remain the subject of theoretical reasoning [5, 6, 7, 8 , 9].

In contrast with the normal white and shiny appearance of the tendons, with tendinopathies, the last one acquire a gray-brown hue. Their shape changes: there are appear the diffuse or spindle-shaped, rounded thickenings. At the same time, the histological research of the tissue does not reveal any signs of inflammation and the presence of its characteristic cells. Disorientation, thickening, and breakdown of collagen bundles against the background of focal growth of vessels, an increase in the number of cells, and an increase in the content of glycosaminoglycans are more likely in favor of the degenerative nature of the processes. So that, the morphological equivalent of the tendinopathy is the term «tendinosis», which is traditionally, but not lawfully, found in some clinical descriptions [10].

In the absence of an inflammatory process and mechanical damage, the reason of the pain syndrome in tendinopathies can be the effect on the nerve endings of chemically active molecules, or neurotransmitters, such as, for example, glutamate, lactate, substance P, which level increases significantly [11, 12].

Often tendinopathies occur without significant clinical manifestations, until a complete or partial rupture of the tendon occurs, which fully corresponds to the development of this pathology in the area of rotator cuff. In those cases when the tendons are surrounded and closely interact with the synovial tissue of paratenon or the mucous bag, in which morphological signs of inflammation may be present, the pain becomes mainly a symptom of paratendinopathy [9]. The latter is observed in the tendon area of the biceps, as well as with subacromial bursitis.

Due to the regulatory effect on the inflammatory process, painkilling and reparative effects, the platelet-rich plasma (PRP) therapy was found to be very popular for the treatment of certain forms of tendinopathy, characterized by a predominance of degenerative processes and weak regenerative potential [13, 14, 15, 16].

The results of treatment of patients with tendinopathies of different localization are determined by a lot of factors, among which the anatomical and biomechanical characteristics of tendons are no less important than the methods of preparation and protocols for using PRP. These circumstances explain not only the greater effectiveness of PRP therapy, for example, with tendinopathy of the Achilles tendon, patellar ligament, extensors of the hand in the area of attachment to the external epicondyle of the humerus, but also persisting doubts about the positive results of using plasma in cases of tendinopathy of

the tendons of the rotator cuff of the shoulder [6 , 14, 17, 18, 19].

In this regard, the results of clinical researches are of particular interest, allowing us to answer the question of the appropriateness of the wider use of PRP-therapy for injuries and diseases of the shoulder joint.

The aim of the research was to estimate the effectiveness of PRP therapy in patients with tendinopathy of the tendons of the rotator cuff of the shoulder and the long head of the biceps of the shoulder.

Materials and Methods

The patients

The material for a multicenter prospective research was observation of the treatment results of 122 patients: 53 men and 69 women aged 46.8±6.8 years with pathology of the shoulder joint, divided into 3 groups: tendinopathy of the rotator cuff (80 patients; 65.6%), subacromial impingement syndrome and tendinopathy of the rotator cuff (20 patients; 16.4%), tendinopathy of the long head of the biceps of the shoulder (22 patients; 18%). The disease of the right shoulder joint was observed in 70 (57%), the left — in 52 (43%) patients.

Patients' examination

Diagnosis of tendinopathies of the shoulder joint and estimation of treatment results were carried out on the basis of patient complaints, physical examination, radiography, ultrasound and MRI.

All patients underwent MRI of the shoulder joint on a high-field tomograph with a magnetic field of 1.5 T (Siemens MAGNETOM Aera), the thickness of the sections was 3 mm. The MRI protocol consisted of obtaining images in three planes: oblique coronary, oblique sagittal and axial using pulse sequences in a T2-weighted image (WI) in gradient echo mode — FFE_T2W, images weighted by proton density — TSE PDW, also using the effect signal suppression from adipose tissue — TSE PD SPAIR.

The treatment technique

Platelet-rich plasma (PRP) was obtained using open or closed cycle techniques by double centrifugation of venous blood without subsequent "in vitro activation" [20].

The local injections of the plasma were prescribed as monotherapy and was carried out three times in 2 ml with a frequency of 1 time in 10-14 days. In tendinopathy of the rotator cuff tendon and subacromial impingement syndrome, accompanied by tendinopathy of the rotator cuff tendon, PRP was injected into the subacromial space, and in cases of tendinopathy of the long head of biceps, into the area of the bicypital groove. For the period of PRP-therapy, some restriction of physical activity was recommended, and physical therapy was prescribed.

Evaluation results

The treatment results were estimated in 1, 3 and 6 months after completing PRP therapy using scores for assessing pain, upper limb function (VAS — visual analogue scale, UCLA — University of California, Los Angeles score, DASH — Disabilities of the Arm, Shoulder and Hand) and instrumental methods (ultrasound, MRI).

The satisfaction of the patients with treatment outcomes was estimated using the modificated scale of verbal assessment (SVAS), according to which the result was distributed from 0 to 3 points: 0 points — unsatisfactory (no improvement), 1 point — satisfactory (movements in the joint improved, pain decreased, function restrictions remain that reduce the quality of life and physical activity), 2 points — good (there are no restrictions in everyday life, intense workload, sports cause pain or discomfort), 3 points — excellent (full recovery, physical activity and sports are possible without restrictions) [21].

The statistical analysis

Statistical processing of the obtained data was performed in the STATISTICA 10 for Windows, using descriptive statistics meth-

ods, comparative nonparametric methods: Mann-Whitney, Kraskel-Wallis. Differences with the criterion $p<0.05$ were considered statistically significant.

Results

At the beginning of treatment, all patients were worried about pain in the shoulder joint, especially in the positions of the hand raised above the shoulder girdle, which lasted more than 3 months and were accompanied by a restriction of active movements. The Neer test with the injection 10 ml of 1% novocaine solution into the subacromial space was positive. There were ultrasound and MRI signs of tendinopathy of the tendons of the rotator cuff and of the long head of the biceps. According to the MRI classification of Scarpone et al [3], tendinopathy of the rotator cuff was classified as grades I and II.

The average platelet count in both open and closed cycles of obtaining PRP was 960±130×10^3/μl. Platelet-rich plasma was also characterized by an increased white blood cell count of 24.7×10^9 / L ± 8.6.

Patients in all three groups had a statistically significant improvement on the scales for assessing pain and function of the shoulder joint compared to their level at the time of initiation of PRP therapy. Reached after 1 month after treatment, the positive effect remained after 3 and 6 months observations (Table 1-3).

Table 1

The shoulder function and outcome results in patients with tendinopathy of the rotator cuff

Scale	Before treatment	1 month	3 months	6 months
UCLA	22,2±3,1	28,1±2,3	31,1±4,3	32,4±4,4
DASH	52,8±4,2	20,1±4,3	18,8±2,6	17,1±5,2
VAS	5,4±0,8	2,4±0,6	1,8±0,4	1,5±0,4
SVAS	–	2,0±0,3	2,1±0,2	2,3±0,2

p = 0,022.

Table 2

The shoulder function and outcome results in patient with subacromial impingement syndrome and tendinopathy of the rotator cuff

Scale	Before the treatment	1 month	3 months	6 months
UCLA	24,4±3,8	28,1±3,1	31,1±4,0	33,0±3,3
DASH	45,6±3,2	11,1±2,7	8,7±2,3	7,8±1,5
VAS	6,6±0,7	2,8±1,3	1,5±0,5	1,3±0,3
SVAS	–	2,0±0,4	2,2±0,2	2,5±0,3

p = 0,006.

Table 3

The shoulder function and outcome results in patient with tendinopathy of the biceps long head

Scale	Before the treatment	1 month	3 months	6 months
UCLA	22,6±2,1	31,7±2,4	32,2±2,8	34,1±3,1
DASH	51,9±3,5	15,1±5,3	8,6±3,3	8,8±2,9
VAS	6,4±0,5	2,6±0,3	1,9±0,2	1,5±0,2
SVAS	–	1,9±0,5	2,1±0,4	2,3±0,3

p = 0,001.

The instrumental methods (ultrasound, MRI) in patients with tendinopathies of the shoulder joint performed before prescribing PRP therapy revealed changes in the tendons of the supraspinatus, infraspinatus muscle and tendon of rotator cuff characteristic of this pathology: swelling of the tendon tissue and the presence of hypoechoic regions in it, the appearance of individual areas with neoplasm of the vessels, swelling of the adjacent mucous bag, accumulation of exudate under the membrane along the tendon.

The control MRI and ultrasound researches of the shoulder joint, performed at different times after PRP therapy, showed positive structural changes in the tendons of the rotator cuff: a decrease or disappearance of edema, the areas of the hypoechoic signal. Around the tendon of the long head of the biceps of the shoulder, in the cavity of the shoulder joint (axillary pocket, back inversion), the amount of free fluid was significantly reduced (Fig. 1-3).

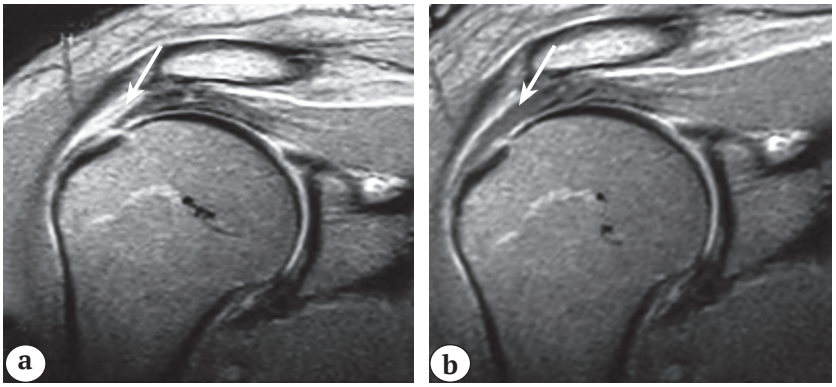

Fig. 1. Changes in the structure of supraspinatus tendon on MRI (indicated by arrow) (PD TSE mode, FOV — 120 mm, section thickness 3.0 mm):
a — prior to treatment;
b — 8 weeks after PRP-therapy

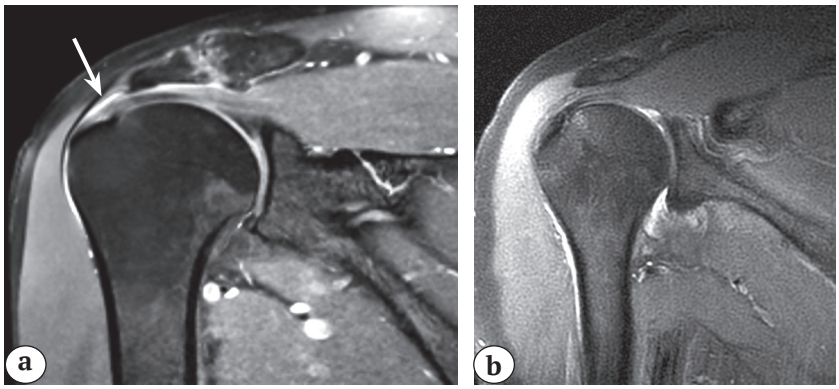

Fig. 2. Changes in the structure of supraspinatus tendon on MRI (indicated by arrow) (PD FS TSE mode, FOV — 120 mm, section thickness 3.0 mm):
a — prior to treatment;
b — 6 months after PRP-therapy

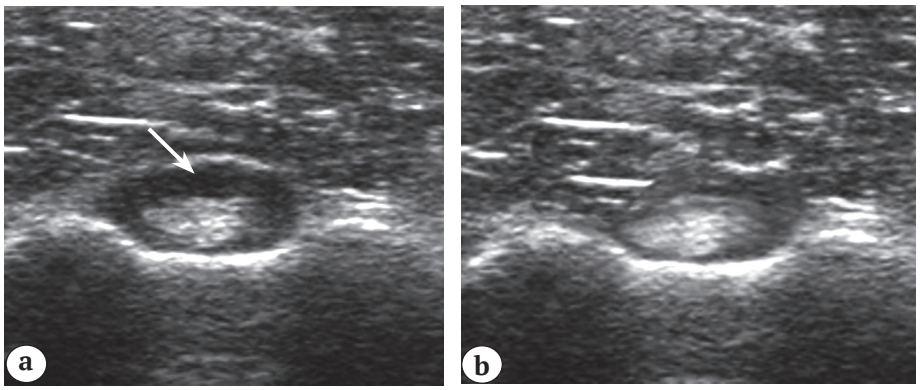

Fig. 3. Changes in echogenicity of LHB tendon on ultrasound (indicated by arrow) (7.5 mHz, linear probe):
a — prior to treatment;
b — 4 weeks after PRP-therapy

Discussion

At the core of the traditional treatment of tendinopathies of various localization is the limitation of physical activity and ensuring the relative immobility of a limb segment, the appointment of physiotherapy, painkillers and anti-inflammatory drugs. And if in the acute stage of the disease traditional therapy is clinically effective, its subsequent pathogenetic effect on the molecular, cellular and other mechanisms of the development of the degenerative process in tendinopathies remains controversial. Often, the resumption of loads, but of lesser intensity, leads to relapse of the pain syndrome and the development of the chronic course of tendinopathy [4, 5,16].

The special PRP properties allow us to consider this blood product as a possible stimulator of physiological and reparative processes in the tendon tissue, which can be equally used in both conservative and surgical treatment of tendinopathies [12, 13, 22, 23].

In separate experimental researches, it was convincingly shown that the growth factors contained in α-granules of PRP platelets are capable of exerting a regulatory effect on all three phases of the inflammatory process by interacting with transmembrane cell receptors and initiating intracellular signals. The influence of the last one on the expression of genes in the nucleus leads to increased synthesis of proteins that regulate the proliferative and synthetic activity of cells. In addition, platelet growth factors stimulate chemotaxis, cell differentiation and local angiogenesis, which is directly related to the repair of damaged tendons [7].

As a result of the interaction of PRP with tendon tissue, a number of authors noted increased proliferation of fibroblasts, synthesis of type 1 and 3 collagen by tenocytes, fibroblasts, migration of progenitor cells from bone marrow to the area of tendon damage, increased size and strength of the regenerate, improved histological and mechanical characteristics of the bone-tendon attachments [13, 14, 15, 22].

The main indicators that are used today to classify various types of PRP are the number of platelets and leukocytes in the resulting plasma. An increase in the platelet count by 4-5 times – up to 1000×10^3 μm/l or close to that in some researches is considered a "visiting card" of PRP [4, 13]. However, the plasma platelet concentration necessary to stimulate the reparative process is not known for certain. Moreover, a number of randomized controlled trials demonstrate the absence of a correlation between the platelet concentration in PRP and the results [16]. This fact is explained by the duality of the effect of growth factors on cell receptors — at a lower concentration of PRP, the stimulating effect is not manifested, at the same time, an increase in platelet concentration above 1000×10^3 μ/l does not lead to further acceleration of regeneration, and even, on the contrary, causes its inhibition [13]. In addition, the activity of some plasma proteins does not depend on the number of platelets (IGF-1, HGF), in contrast to the concentration of those (PDGF, TGF-β1, VEGF, EGF, bFGF), which directly correlates with the number of platelets. Finally, it was found that cell viability and proliferation decreases at high concentrations of PRP, but increases at lower concentrations [24].

Views on the content of leukocytes in PRP can be considered more or less consistent, since the ratio of platelets/leukocytes in the injected plasma reflects the balance of developing anabolic and catabolic processes in the tissues. In plasma with a high white blood cell count, the number of pro-inflammatory mediators increases, leading to inflammation, which has a stimulating effect on the course of reparative processes in a number of chronic conditions, including tendinopathies [25, 26]. Individual leukocyte fractions, such as mononuclear cells (lymphocytes, monocytes), can have a positive effect on the activity of growth factors, since they are associated with many bioactive molecules and

even include progenitor cells (CD34 +) [27]. It is not surprising that the positive results of treatment of tendinopathies of different localizations in most studies were associated with the introduction of PRP with a high content of leukocytes [28]. The problem is only in obtaining plasma with a given number of leukocytes and monitoring the clinical manifestations of the inflammatory process in the first few days after injection due to the known difficulties in separating leukocytes from platelets without significant loss of the latter. In our study, we used PRP with a high white blood cell count (24.7×10^9 / L ± 8.6), but the pain and limitation of the function of the shoulder joint in the first few days after the administration were not pronounced.

In our research, the patients with shoulder joint tendinopathies were given PRP with a platelet content close to 1000×10^3 μ/l. A fourfold increase in platelet count in plasma was also preferred by most researchers, which made it possible to compare the results [28].

One of the important question of PRP-therapy is the technique of manipulation itself. The using of ultrasound control improves the accuracy of the location of the injection needle in the projection of the tendon and gives great guarantees for plasma to enter the region of altered tissues [18]. The introduction of plasma over the area of the pathological focus or around it (the technique of "sprinkling with pepper") is preferred in most researches [18, 28, 29]. In the event that ultrasound control is not used, the injection needle is located in the subacromial space, taking into account the topography of the tendons of the rotator cuff, as it was done in our and a number of other studies. The idea of transferring the technique of intra-tendon injection of plasma, which turned out to be quite successful in the treatment of tendinopathy of the ligament of the patella and tendon of the quadriceps femoris, on the tendons of the rotator cuff does not yet find wide support due to the risk of structural damage to the relatively denser tendon tissue of the last localization [12, 26].

The results of clinical trials on the use of PRP in various forms of tendinopathy in general and tendinopathy of the rotator cuff in particular do not look as definite as their experimental equivalents. A probable reason for this may be the diversity of the contents of the resulting PRP and plasma application protocols. One cannot ignore the features of different tendons with their anatomical and biomechanical characteristics [4, 13].

In a prospective study by M Scarpone et al, it was shown that injections of PRP (platelet count — $895\pm204\pm10^3$/μl) into the subacromial space significantly improve pain, shoulder joint function, and also MRI-structure of the tendon for 3 months after completion of treatment [3]. The level of pain reduction (7 times) to 52 weeks. after treatment, it turned out to be slightly higher than the similar indicator obtained in our study (5 times), and testified to the preservation of a positive effect in a longer observation period. Patient satisfaction with PRP therapy (94%) was also close to the results obtained in our study.

D.W. Rha et al. also reported the positive results from PRP therapy in a prospective randomized research of 39 patients divided into 2 groups. Twice injections of PRP (platelet count — 600×10^3/μl) with a 4-week interval and the use of «pepper sprinkling» under ultrasound control significantly reduced pain and functional impairment compared to the group of patients who used a dry needle within 6 months observations [18].

In a comparative research by L. von Wehren et al, including 50 patients with tendinopathy and partial injuries of the tendon of the supraspinatus muscle of the shoulder, divided into 2 groups depending on a single injection into the subacromial space PRP (platelet count — 412×10^3/μl) or corticosteroid (triamcinolone acetonide, crystalline suspension), after 6 and 12 weeks, the results were significantly better in the PRP group. Moreover, a decrease in the severity of pain, an improvement in the function of the shoulder joint continued throughout the observation period, which was also noted in

our research. However, by 6 months after the start of treatment, the estimated parameters in both groups of patients did not have statistically significant differences. The last one also applied to the MRI assessment of signs of tendinopathy according to the classification of M. Scarpone et al, who had obvious positive dynamics in both groups of patients [19].

In contrast, in a randomized double-blind research by S. Kesikburun et al., which included 40 patients, divided into two equal groups — PRP (platelet count — 964×10^3/μl) and 0.9% NaCl, a significant difference in the estimates pain syndrome, shoulder joint function and quality of life of patients during the year of observation was not observed. It should be noted that all patients received only a single injection into the subacromial space. Since patients of both groups received therapeutic physical training complex for 6 weeks, the authors concluded that PRP therapy in the treatment of tendinopathy of the rotator cuff is not more effective than therapeutic physical training [17]. The results obtained by S. Kesikburun et al. are also supported by a meta-analysis of randomized trials of the clinical efficacy of PRP therapy in comparison with the placebo and dry-needle groups by K. Tsicopoluos et al. After 6 months after the start of treatment, the difference in the severity of pain and functional disorders was slightly better in patients receiving PRP therapy [23].

In a recent systematic review by G. Filardo et al on PRP therapy for tendon diseases, an analysis of 8 publications, the majority of which corresponded to the first level of evidence, was devoted to the problem of conservative treatment of tendinopathy of the rotator cuff. The results of 5 researches showed a positive effect of PRP on the course of the disease in the early and medium-term observation periods. Three authors showed an uncertain or even negative result regarding the effectiveness of PRP therapy [29]. However, most of the authors, to whose opinion we also join, were unanimous in their conclusion that PRP therapy for shoulder joint tendinopathies can be attributed to safe biological treatment methods, the indications of which still need to be clarified [13, 15, 28, 29] .

The main defect of the presented study is the absence of a control group of patients treated with one of the traditional methods, or the «placebo» group with the introduction of a 0.9% NaCl solution into the subacromial space.

The clarification of indications and justification of the wider use of PRP-therapy requires prospective controlled researches for each of the nosological forms in the pathology of the shoulder joint.

So that the PRP therapy in patients with tendinopathy of the rotator cuff and of the long head of the biceps of the shoulder, subacromial impingement syndrome with tendinopathy of the rotator cuff reduces the severity of pain and improves the function of the shoulder joint with positive dynamics that lasts from 1 to 6 months observations.

Publication ethics

All patients signed voluntary informed consent for examination and treatment.

The ethical examination of this study was carried out by Local ethical committee (protocol No. 2131A — 2017 of May 03, 2017).

Competing interests: the authors declare that there are no competing interests.

Funding: state budgetary funding.

Authors' contribution

Malanin D.A. — analysis of literary sources, the formation of a hypothesis, a statistical analysis of the material, the formulation of scientific provisions.

Norkin A.I. — collecting of material and preparing a database.

Tregubov A.S. — collecting material and preparing a database, statistical analysis of the material.

Demeshchenko M.V. — collection of material and preparation of the database.

Cherezov L.L. — statistical analysis of the material.

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