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Original Article

Efficacy of ultrasound guided platelet-rich plasma in the repair of partial and full-thickness supraspinatus tears

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Abstract: Background: Rotator cuff tears [RCT] are one of most common shoulder pain causes. Some patients do not give response to conservative treatments and patients couldn't get sufficient recovery after the surgery. Ultrasound guided platelet-rich plasma [PRP] administration may decreases the RCT sourced pains and improves functional abilities in patients with partial and complete rotator cuff tear. In this control group included study, the effectiveness of PRP treatment on RCT's has been revealed. Methods: In this randomized controlled clinical trial, the study included 90 patients who were randomized to four groups as: partial tear PRP, partial tear control, complete tear PRP and complete tear control. One cc PRP was obtained from 20 cc blood samples of patient, after double centrifuged at 400 g for 10 minutes. Under musculoskeletal ultrasound guidance, the PRP groups were given 3 injections of PRP in the affected shoulder at 3-week intervals. All groups were given a home exercise program 3 times per week. The range of motion, Quick DASH, Shoulder Pain and Disability Index [SPADI], Constant and VAS scores were used for the evaluation of patients at 3, 6 and 9 weeks, and 3, 6 and 12 months for follow-up visits. Results: In all groups, statistically significant improvements were observed in ROM, Quick DASH, SPADI, Constant and VAS scores [$P < 0.05$] at 12 months. Compared to control groups, more prominent improvements in all these clinical parameters were seen in PRP groups [$P < 0.001$]. It was also observed that the improvements seen after their first injection in PRP patients had persisted at 12 months. There was no significant difference in their improvements in these clinical parameters between PRP injected patients with partial RC tear and PRP injected patients with complete RC tear. Conclusion: We found significant and sustained improvement in pain and functional outcomes in PRP treated patients with RC tear. Our results suggest that PRP is the powerful treatment option in both patients with partial and complete RC tear and it may be an alternative approach before surgery in patients that do not benefit from conservative treatments.

Keywords: Platelet-rich plasma, rotator cuff, rotator cuff tear, supraspinatus

Introduction

Rotator cuff disorders account for 10% of the causes of shoulder pain [1]. Supraspinatus tears are one of the commonly encountered rotator cuff disorders. This disorder unfavorably affects the quality of life of patients, leading to reduced range of motion of the joint and muscle strength [2, 3]. It can occur as a result of traumatic or degenerative processes. Its prevalence peaks at an advanced age.

Rotator cuff tears can be treated using conservative or surgical treatments. Surgical treatment options include open, mini-open or arthroscopic [single-row and double-row suture, transosseous] methods [4]. Several studies have shown no superiority of one method to another [4]. Many factors are involved including surgical method used in tendon repair and patient characteristics [5]. The studies have also shown that 50% of the patients did not show complete recovery regardless of the surgical method employed [6].

Although recently introduced methods have reduced the risk of re-rupture after surgery, tendon healing below the desired level has prompt-

Table 1. Patient Screening Criteria

Inclusion Criteria	● Age between 20-65 years
	● VAS score > 4 for 3-12 months
	● Loss of more than 25% in the range of joint motion
	● Positive in at least one of Jobb, Lift off, Speed, Yergeson, O Brien's, Drop arm test or had Poppeye's sign
	● Confirmed supraspinatus tears on MRI and classified as partial or full thickness tears
	● Not responded to conservative therapy for at least 3 months
Exclusion Criteria	● Uncontrolled systemic disorder
	● History of rheumatic disease
	● Active malignancy
	● History of a surgery to the affected shoulder, manipulation, mobilization or arthroscopy
	● History of steroid, local anesthetics or hyaluronic acid injection, kinesiotaping, prolotherapy or neural therapy over the last 3 months
	● Reflex sympathetic dystrophy or neurodeficit of the effected extremity
	● Anemia or thrombocytopenia (hemoglobin < 12 g/dl, platelet < 150.000/uL), bleeding disorders, patients using anticoagulant or antiagregant medications
	● History of medication use over a period of 10 days before and after treatment
	● Infection or suspicious of infection
	● Serious psychiatric disorder

ed researchers to search for alternative methods such as platelet-rich plasma (PRP) administration [4]. The studies used PRP administration before and after arthroscopy and although they showed a decrease in the risk of re-rupture and increased healing in partial tears, clinical and radiological efficacy has not been established yet [7-13]. The aim of the present study was to evaluate the efficiency of ultrasound guided PRP administration in improving clinical parameters such as pain, Quick DASH, SPADI and Constant score in patients diagnosed with partial or full-thickness supraspinatus tears.

Materials and methods

This was a prospective, randomized and comparative clinical trial. The study protocol was approved by the Ethics Committee. A written informed consent was obtained from each participant. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient selection, sampling and randomization

All patients admitted to Outpatient Clinic of the Department of Physical Therapy and Rehabilitation between January 1, 2014 and December 31, 2014 with a diagnosis of rotator cuff tear were screened for participation. Primary outcome was ımprovement ın Constant score in partial PRP, full-thickness PRP and control groups after 12 months fallow up. Secondary outcome was efficacy of PRP as an alternative treatment before surgery in patients who do not respond to conservative treatment with WAS score, Quick dash, shoulder pain disease activity, need for surgery. Our sample size was based on difference of Constant scores between two groups with power of 80%, a false-positive rate of 5%, and we required 30 patients per treatment arm [14]. A total of 118 patients were evaluated clinically and radiologically for inclusion and exclusion criteria shown in **Table 1**.

A total of 90 patients were included to the study and the patients were randomized into partial-PRP, full-thickness-PRP and control groups using closed envelope method. Each group consisted of 30 patients. There was no difference between groups in demographic data of the patients (**Table 2**).

PRP preparation protocol

A laboratory study was conducted to determine protocol in obtaining PRP. Fresh whole blood obtained from the blood bank was used for this purpose. After transferring the blood samples into 20-cc sterile tube under laminar flow, samples were processed by mono and double centrifugation at 200, 400, 600 and 800 g [15, 16]. Each protocol was repeated four times and approximately 1 cc PRP was obtained from

Table 2. Demographic data of the groups

		PARTIAL PRP n=30	PARTIAL CONTROL n=15	FULL-THICKNESS PRP n=29	FULL-THICKNESS CONTROL n=15
Age (Mean ± SD) (year)*		50,43 ± 9,41	50 ± 9,14	53,35 ± 9,46	57,27 ± 8,56
Gender, n (%)*	Female	11 (36, 7)	12 (80, 0)	25 (86, 2)	11 (73, 3)
	Male	19 (63, 3)	3 (20, 0)	4 (13, 8)	4 (26, 7)
Educational* Status, n (%)	Illiterate	1 (3, 3)	1 (6, 7)	3 (10, 35)	4 (26, 67)
	Primary School	17 (56, 7)	11 (73, 3)	21 (72, 41)	10 (66, 67)
	High-School	3 (10, 0)	1 (6, 7)	5 (17, 24)	1 (6, 67)
	Higher Education	9 (30)	2 (13, 3)	0 (0)	0 (0)
Marital status, n (%)*	Married	28 (93, 3)	14 (93, 3)	89,7	86,7
	Single	2 (6, 7)	1 (6, 7)	10,3	13,3
Occupational risk (Yes/No)*	Yes	6	1	3	3
	No	24	14	26	12
Trauma (Yes/No)*	Yes	17	6	19	8
	No	13	9	10	7
Systemic disease (Yes/No)*	Yes	13	6	17	7
	No	17	9	12	8
Affected Shoulder*	Right	13	6	22	11
	Left	17	9	7	4
Dominant Shoulder*	Right	25	15	29	14
	Left	3	0	0	1
Duration of Disease (Mean ± SD) (month)*		5,97	4	7,03	4,2
Night pain, n (%)*		29 (96, 7)	15 (100)	26 (89, 7)	14 (93, 3)

*Fisher's Exact test and Pearson Chi-Square test $p < 0,05$.

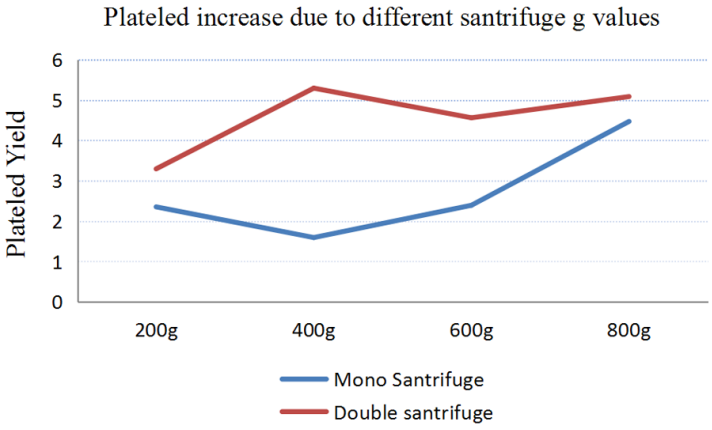

Figure 1. Platelet yields following mono and double centrifugation at different g levels.

each protocol. PLT count was determined in the complete blood count device. Increases in the amount of platelets after mono and double centrifugation at different g values are shown in **Figure 1**.

A total of 32 samples were obtained and the PRP samples were then stored at -80°C. The samples were activated with 10% $CaCl_2$ for 30 min [15], platelet activation was tested with the level of P-selectin using and growth factors that were analyzed including vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin like growth factor [IGF], platelet derived growth factor (PDGF), transforming growth factor beta (TGF-β) platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), transforming growth factor beta (TGF-β) and insulin like growth factor (IGF) by ELISA method [17]. The mean levels of growth factors are listed in **Table 3**.

As the studies have recommended a 3 to 5-fold increase in platelet yield and a platelet count of 1,000,000 per 5 ml of plasma volume in order for a sample to be considered PRP [18, 19], platelet yield at very high concentrations was shown to inhibit regeneration [20] and platelet fragmentation rate is known to increase at forces above 800 g [21, 22] double centrifugation at 400 g each for 10 min was selected as the method of obtaining PRP.

Table 3. P selectin and growth factor levels at different g levels after mono and double centrifuge

		P selectin ± SD [ng/ml]	VEGF ± SD [pg/ml]	EGF ± SD [pg/ml]	IGF ± SD [ng/ml]	PDGF ± SD [pg/ml]	TGF-β ± SD [pg/ml]
200 g	Mono centrifuge	2,87 ± 1,11	1336,06 ± 198,81	67,57 ± 12,52	18,70 ± 1,56	27528,45 ± 3662,79	15394,04 ± 1217,73
	Double centrifuge	2,26 ± 0,11	6664,57 ± 502,4	379,27 ± 14,46	19,74 ± 1,94	91446,50 ± 5808,79	16175,49 ± 7406,25
400 g	Mono centrifuge	2,04 ± 0,46	2502,59 ± 377,72	110,60 ± 19,6	16,43 ± 2,38	38179,85 ± 11618,23	2988,78 ± 191,30
	Double centrifuge	2,57 ± 0,34	10381,33 ± 413,1	388,91 ± 9,68	19,96 ± 2,79	190927,96 ± 36619,33	8386,72 ± 1540,94
600 g	Mono centrifuge	3,07 ± 0,86	5031,69 ± 485,79	212,70 ± 21,73	14,90 ± 1,66	134090,24 ± 89834,78	15357,10 ± 5817,64
	Double centrifuge	2,64 ± 0,44	4510,33 ± 960.01	198,76 ± 53.3	22,39 ± 1,46	354313,56 ± 117672,63	15199,06 ± 7761,36
800 g	Mono centrifuge	3,46 ± 1,10	5727,53 ± 397,97	191,91 ± 38.62	16,12 ± 4,29	59618,94 ± 13366,02	11276,95 ± 4210,81
	Double centrifuge	2,18 ± 0,10	9245,67 ± 5195.24	276,19 ± 139.2	16,03 ± 0,61	211616,01 ± 7331,98	10437,75 ± 2472,14

Administration of PRP to the patients and clinical follow-up

Assessment of patients in follow up visits and injections were performed by the same physician. The physician was not blinded and knew whether the patient was in PRP or control group. A 20-cc blood sample was obtained from the patients in the full-thickness and partial tear groups, and the samples were transferred into 10-cc sterile sodium citrate tubes [18, 20]. After centrifugation at 400 g for 10 min, supernatant plasma was transferred into a sterile 10-cc tube, further centrifuged at 400 g for 10 min, and PRP was prepared from the lower one third portion (approximately 1 cc) of the centrifuged plasma [9, 18, 23]. Although the platelets were activated in our previous laboratory study that measured growth factor levels, no activation was performed before applying to the RC tear area because platelets were believed to be activated after injection and contact with collagen tissue. All fluid transfers during preparation of PRP were conducted under laminar flow to extract a PRP purified from the pathogens. Using a 21 G needle, PRP was injected into the area of intratendinous tear in ultrasound guidance using out of plane method. This procedure was performed every three weeks in a total of three times in company with an experienced radiologist who specifically works on ultrasonography of the musculoskeletal system. The injections were carried out by the same physician accompanied by the same radiologist. The patients were recommended to perform Codman exercises, range of joint motion exercises, and isometric strengthening exercises three days a week. The patients in the control group were only followed with an exercise program performed three days a week and they were avoided to use non-steroid anti-inflammatory drugs (NSAIDs) 10 days before and after injections. Paracetamol and cold presses were allowed in the presence of pain. The patients were advised to avoid lying on the painful shoulder and repetitive movements above the head level and they were not allowed to receive other means of physical therapy during the study.

The first injection was administered at week 0, second injection was administered at week 3, and last injection was administered at week 6. The patients were evaluated using Visual Analogue Scale [VAS] score, night pain, Constant Shoulder Score, Shoulder Pain Disability Index, Quick-DASH questionnaire with respect to range of joint motion, side effects, complications and need for surgery before the injections, at week 3 after the first injection, week 6 after the second injection, week 9 after the third injection, and at month 3, month 6, and month 12.

Statistical analysis

The statistical analysis was performed using the SPSS version 22.0 for Windows software (IBM Corp., Armonk, NY, USA). A patient from partial rupture PRP group that underwent surgery after third injection was excluded from the study. Analysis in partial PRP group was performed in 29 patients. However, patients with partial and full-thickness tears in the control group were analyzed separately during statistical analysis. Consolidated standards of reporting trials (CONSORT) flow diagram was shown in **Figure 2**.

The Fisher's exact and Pearson's chi-square tests were used to compare categorical variables related to demographic and clinical features between the groups. The repeated measures analysis of variance (ANOVA) was used in intragroup comparisons indicating to what extent numeric values were changed by the therapies administered during the treatment period. The repeated measures ANOVA was used to compare numeric variables between the groups. Covariate analysis was performed in case of a significant difference in a certain parameter from baseline. Post-hoc Bonferroni analysis and Dunnet T3 tests were performed to find out parameters that showed significant differences were significantly different between which groups. A p value < 0.05 was considered statistically significant. Results were checked with intend to treat (ITT) analysis after adding excluded patient.

Results

All groups showed significant improvements ($p < 0.05$) in all measures: VAS score, Constant Shoulder Score, Quick-DASH, Shoulder Pain Disability Index, total pain score, total disability score and range of motion (**Figures 3**-**6**).

However, partial PRP and full-thickness PRP groups showed strongly significant healing from

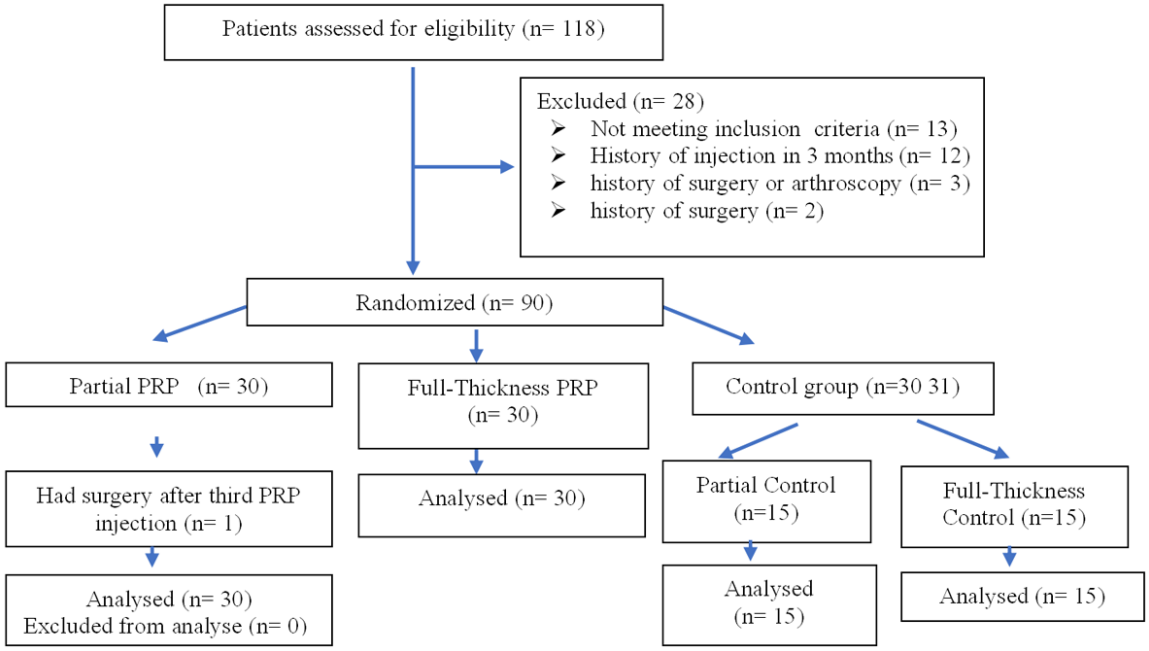

Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

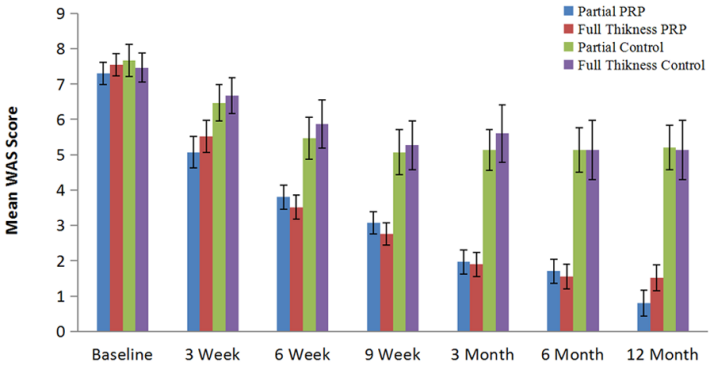

Figure 3. The change in WAS score after administration of platelet-rich plasma.

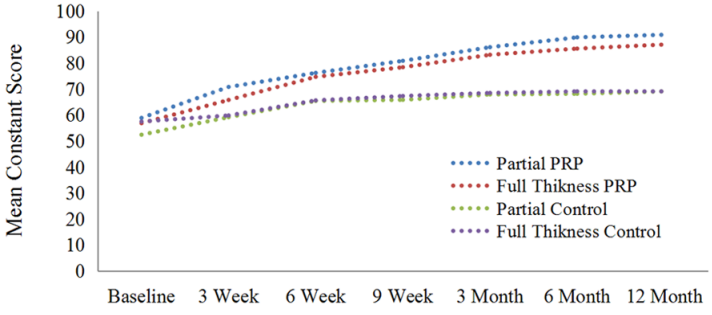

Figure 4. Change in Constant score in one year follow up.

the first injection (P: 0.001), and treatment efficiency was only observed after 6 weeks in the control groups. Well-being was significantly sustained even at 12 months in the PRP group (P: 0.001). A significant decrease in VAS scores was detected in PRP groups at week 3 and the improvement sustained at one year follow-up. There was a significant decrease in night pain at average three months in the PRP groups ($p < 0.05$). Except internal rotation (P: 0.101) in partial control group, abduction (P: 0.079) and external rotation (P: 0.302) in complete control group there was significant improvement in ROM in all groups at 12 months follow-up ($p < 0.05$).

Table 4 shows the comparison of all groups to indicate which group benefited from the treatment the most. When partial control group was compared with partial PRP group, PRP-treated group showed better improvement in all assessed parameters (P: 0.001). When full-thickness control group was compared with the full-thickness PRP group, PRP-treated group showed better improvement in all parameters with the excep-

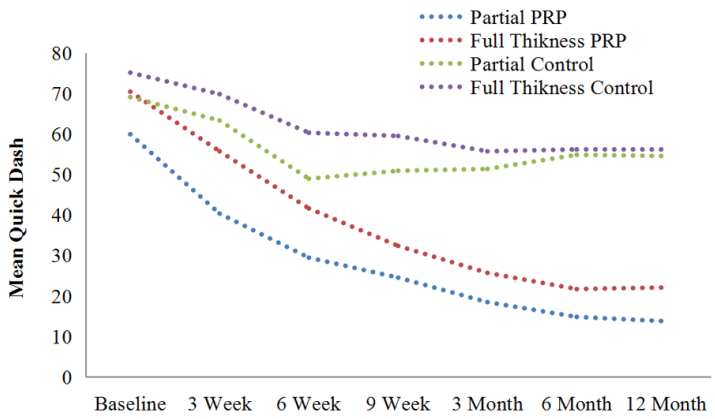

Figure 5. Change in Quick Dash in one year follow up.

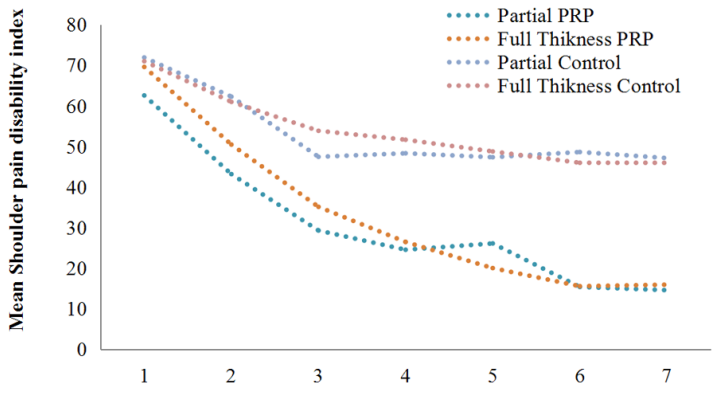

Figure 6. Change in Shoulder Pain Disability Index in one year follow up.

tion of increase in flexion and abduction angles (P: 0.001). When full-thickness PRP and partial PRP groups were compared, patients in the partial and full-thickness tears groups benefited almost equally from the PRP therapy ($p > 0.05$). When full-thickness control and partial control groups were compared, patients in the partial and full-thickness tear group benefited almost equally from the exercises ($p > 0.05$). Results were checked after adding excluded patient with ITT analysis and PRP was found to be effective for both partial and complete tears comparing with control group (P: 0.001).

During the study, only one patient in the partial PRP group required surgical intervention. Temporary increase in the intensity of pain that lasted average three days and occurred in 16 patients was the most common side effect. The patients with side effects were treated with paracetamol, cold pack and their symptoms disappeared in 3-7 days. Three patients experienced hypotension and sweating. These symptoms were attributed to the injection itself and no other complications occurred during follow-up.

Discussion

Biological augmentation therapy has been studied extensively in rotator cuff pathologies; the reason is that patients frequently suffer re-rupture although initial surgery may provide healing [22]. Although pain relief and functional improvement can be obtained after surgery, re-rupture has been observed in about 11-95% of patients during 2-years followup [8, 9]. Fibrotic scar tissue has been deemed responsible for the occurrence of a new rupture caused by incomplete tissue healing [10]. This has raised the question of how healing of the tear could further be enhanced and this has prompted studies on PRP therapy [24, 25]. As studies about PRP administration were designed, questions were increased about efficacy, efficacy duration and safety. Some authors did not suggest routine use of PRP therapy as there is no sufficient evidence for healing, although it may provide pain relief [26, 27]. On the other hand, other authors reported that PRP therapy may improve healing in small and medium-sized tears although the results were insignificant for massive tears, and they recommended the use of PRP therapy [28].

Randelli et al. [11] found PRP therapy to be an effective and safe method. These effects were shown to be sustained up to 24 months. In the present study comparison of PRP and control groups showed significantly better healing in the PRP groups as assessed by VAS score, Constant Shoulder Score, Shoulder Pain Disability Index, Quick-DASH and range of joint motion. This finding supports the notion that patients receiving PRP therapy benefit more from the therapy. Significant difference was observed between the parameters in the PRP groups as from the very first injection, whereas significant healing effect in the control groups

Table 4. Comparison of clinical parameters between the groups

	Significance	Partial PRP/ Partial Control	Partial PRP/ Full-thickness PRP	Partial PRP/ Full-thickness Control	Partial Control/ Full-thickness PRP	Partial Control/ Full-thickness Control	Full-thickness PRP/ Full-thickness Control
VAS#	P < 0,001	P: 0.004*	p > 0,05	P: 0,02*	P: 0,004×	p > 0,05	P: 0,001×
Constant# Shoulder Score	P < 0,001	P < 0,001	p > 0,05	P < 0,001	P < 0,001	p > 0,05	P: 0,001
Quick Dash#	P < 0,001	P < 0,001*	p > 0,05	P < 0,001*	P: 0,019×	p > 0,05	P < 0,001×
Shoulder Pain# Disability Index	P < 0,001	P: 0,001*	p > 0,05	P: 0,001*	P: 0,006**	p > 0,05	P: 0,003×

#Bonferoni test. *Significant to the favor of partial PRP **Significant to the favor of partial control. ×Significant to the favor of full-thickness PRP.

was observed only after 6 weeks. Improvements in the parameters were sustained at one-year control visit in both PRP and control groups. These data indicate rapid onset of action for PRP in rotator cuff tears and significant healing even after the first injection and healing effect was sustained at one year. The present study supports the methods safety that do not report serious side effect or complication other than hypotension, syncope and temporary increase in the pain intensity that were attributed to the injection itself.

Another question is which patients benefit most after application partial tear or full-thickness tear? Holtby et al. [16] showed that PRP administration during arthroscopy in small and medium-sized tears had short time effect on perioperative pain and outcome measures in their randomized controlled double blinded study. There was no certain data about efficacy of PRP in patients with full-thickness tear. The present study however did not show significant differences between partial PRP and full-thickness PRP groups with respect to VAS score, night pain, Constant Shoulder Score, Quick-DASH, and shoulder pain disability index. In the light of these data, both groups benefited equally and PRP therapy is worth administering regardless of whether it is a full-thickness or partial tear.

The studies did not reach a consensus regarding timing and method of PRP administration in patients undergoing rotator cuff repair. In previous studies, PRP was generally administered during or after arthroscopy. Meta-analyses have failed to demonstrate the efficiency of PRP administration during arthroscopy [27, 29]. Previous studies on the use of PRP in rotator cuff surgery have yielded controversial results; however, while processing this information, we must consider the facts that outcomes of surgery are already unsatisfactory and healing in the footprint area is poor due to limited blood supply [5]. Platelet-rich plasma was administered during arthroscopy until the studies by Kesikburun, and Wehren and Shams. Kesikburun et al. [30] administered PRP and isotonic solution into the subacromial area in 40 patients with partial supraspinatus tears in the guidance of ultrasonography, and clinical recovery in the PRP-treated group was not significantly superior to the other group. On the other hand, Wehren [31] and Shams [32] administered steroid or PRP injections in patients with partial supraspinatus tears using the subacromial injection technique. The patients were evaluated using constant shoulder score, ASES, SST and VAS score and they found more significant healing in the PRP group. Also Sengodan et al. [33] applied PRP in 20 patients with RC tear and showed ultrasonographic improvement with better clinical results. These studies have raised the question whether PRP administration without performing surgery would provide satisfactory outcomes and the results of the present study support this hypothesis.

One of the most important issue is PRP's place in RC tears treatment diagram. In the present study patients unresponsive to three-month course of conservative therapy were included in the control groups; all groups received exercise therapy three days a week and all patients were advised to avoid repetitive-forced movements above the head level. Both partial control and full-thickness control groups having benefited from the therapy and presence of no significant difference between these groups support the notion that exercise is the basis of therapy in patients with rotator cuff tears. It is important that the treatment approach should include elimination of factors causing shoulder pathology and administration of appropriate exercise therapy. However, it is obvious that concurrent PRP injection supplied significant improvement in VAS score, night pain, Constant Shoulder Score, Quick-DASH and shoulder pain disability index. It therefore seems more reasonable to administer PRP therapy to patients that are unresponsive to conservative therapy but before surgery.

Also there is not a consensus about preparation method, leucocyte rich or poor PRP to use, platelet count and activation of PRP. In the present study 1 cc leucocyte rich PRP administration was performed without platelet count and activation as platelets are thought to be activated when they had connection with collagen tissue. Although the mean number of platelets and level of growth factors achieved at each g had been previously analyzed in our preliminary laboratory study, no platelet and leucocyte count was performed during this study. Some authors have suggested that PRP preparation using lower g force and longer centrifugation time would yield platelet-rich fibrin (PRF), which might trigger healing and create an

appropriate surface for the adhesions of molecules. In following years, physiatrists may prefer PRP and surgeons may prefer PRF to enhance adhesion. Some authors expressed that it is unclear whether appropriate healing is induced by administering growth factors into the site of tear through PRP administration (without fibrotic scar tissue formation). This has raised that question whether appropriate healing could be induced if undifferentiated stem cells are administered together with PRP [28]. In the future, PRP plus stems cell administration may be introduced into treatment methods in the treatment of rotator cuff tears.

According to results of the present study platelet-rich plasma therapy was found to be an effective and safe method and the effects of therapy were shown to be sustained for 12 months. It is believed that PRP supplies this clinical improvement through growth factors released from the granules and attracting inflammatory cells to the site of injury through chemotaxis and inducing proliferation and angiogenesis in the tenocytes, stem cells and endothelial cells [34]. Although there are controversial data regarding PRP administration during arthroscopy in rotator cuff tears, it is stipulated that PRP might be preferred as an alternative treatment method before proceeding to surgery with accumulating studies and data related to PRP administration to the target point. Widespread use of these methods may provide improvement in pain, night pain and functional status. The rate of ensuing surgery or risk of re-rupture might be reduced. Thus, it is possible to assume that these methods might expedite return to work in actively working patients with rotator cuff tears and reduce treatment costs.

The limitations of the study include small sample size. Large-scale, randomized, controlled clinical studies are, therefore, warranted. Although preliminary study determined which g level provides how much increase in the platelet yield and growth factor levels, it is difficult to ensure standardization and homogeneity in all patients. Heterogeneity in this regard is one of the most important limitations. As injections were performed by the same physician and radiologist and they were not blinded, there may be a bias in evaluation of efficacy. Randomized controlled, double blinded, may be placebo controlled studies by injecting isotonic saline solution should be designed in the future. Also the efficacy, tear volume, rerupture should be evaluated radiologically in further studies.

Conclusion

In conclusion, PRP administration in patients with partial or full-thickness supraspinatus tears unresponsive to conservative therapy produced statistically significant favorable effects with respect to VAS score, Constant Shoulder Score, Shoulder Pain Disability Index, Quick-DASH, and range of joint motion. These effects occurred at as early as three weeks after the first injection and were sustained up to one year. There was a significant decrease in night pain at three months. Patients with full-thickness and partial tears benefited equally. In the light of these data, PRP is an effective and safe method and can be considered before surgery; however, larger-scaled randomized, controlled and double blinded clinical studies are required.

Disclosure of conflict of interest

None.

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