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What is better for rotator cuff tendinopathy: dextrose prolotherapy, platelet-rich plasma, or corticosteroid injections? A randomized controlled study

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Abstract

Background: Rotator cuff tendinopathy (RCT) is a leading cause of shoulder pain and disability. Management is mainly conservative, but the limited ability of tendons to regenerate is the main cause of unsatisfactory results. So, we conducted our study to compare the efficacy of deep prolotherapy (glucose 25%), platelet-rich plasma (PRP), and betamethasone corticosteroid for treatment of RCT to find the most effective one based on clinical, functional, and radiological assessment.

Results: Regarding visual analog scale (VAS), it was significantly ($p < 0.001$) improved after injection among group 1 (prolotherapy group) and group 3 (steroid group) patients, while no significant improvement was noted among group 2 (PRP group) ($p = 0.212$) patients. The Western Ontario Rotator Cuff (WORC) Index significantly improved among the studied groups ($p < 0.001$, $p = 0.049$, and $p < 0.001$, respectively) after injection. Regarding the range of motion (ROM), a significant improvement ($p = 0.029$) was achieved in group 1 after injection but no significant improvements were noted among group 2 and 3 patients ($p = 0.529$ and 0.121 , respectively). There was a significant improvement among group 1 and 2 patients ($p < 0.001$ and $p = 0.020$, respectively) regarding the grade of tendon lesions but no improvement occurred among group 3 patients ($p = 0.470$).

Conclusion: Prolotherapy injections improve shoulder ROM, VAS, WORC index, and rotator cuff tendon healing while PRP injections improve WORC index and tendon healing but steroid injection has no effect on healing.

Trial registration: [PACTR202005610509496](https://www.pactr.org/registration/202005610509496). Retrospective registration on May 25, 2020, Pan African Clinical Trial Registry.

Keywords: Rotator cuff tendinopathy, Prolotherapy, Platelet-rich plasma, Corticosteroids

Background

Rotator cuff tendinopathy (RCT) or rotator cuff disease (RCD) is a leading cause of shoulder pain and a significant source of disability and loss of work. It is a common disorder, and its prevalence increases with age and with occupations involving overhead activities [1].

Sometimes, tendon healing is unsatisfactory with the resultant tendinosis which progresses to partial tear then full-thickness tear. Histopathological study of chronic tendinopathy showed a disturbance in collagen fibers with increased vessel number and leukocyte count denoting inflammatory reaction in chronic tendinopathy [2]. RCT can be diagnosed by musculoskeletal ultrasound (MSUS) as it is rapid, inexpensive, non-invasive, has virtually no side effects and allows the rotator cuff to be visualized dynamically [3].

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Management of RCD without full-thickness tear is mainly conservative in addition to physiotherapy, manipulation, and non-steroidal anti-inflammatory drugs (NSAIDs) which show a high rate of recurrence and persistent pain due to the limited ability of rotator cuff tendon to regenerate leading to chronic tendon disease [4].

Prolotherapy is the injection of an irritant agent, most commonly a hyperosmolar dextrose solution, at multiple painful entheses. It initiates an inflammatory cascade at the site of injection, which causes fibroblast proliferation with subsequent collagen synthesis resulting in a stronger tendon or ligament. Also, it may act as a central pain modulator [5].

It is known that healing is a highly complex biological process and various factors are required [1]. So, the potential for the use of platelet-rich plasma (PRP) is increased, which is a centrifuged blood product that contains a supra-physiologic amount of platelets, containing several cytokines and bioactive factors including basic fibroblast growth factor (FGF2), vascular endothelial growth factor, and transforming growth factor β (TGF). It is implicated in improving proliferation and collagen secretion of tenocytes promoting tendon cell growth and decrease oxidative stress which lead to cell apoptosis. Although it is easily applicable in conservative or augmentation of healing after surgical repair, studies were inconclusive [6].

Local corticosteroid injections are potent anti-inflammatory drugs improving local tissue metabolism with pain relief. Despite extensive research, the effectiveness of steroid injection in RCT is still questionable [7].

The aim of the present study was to compare the efficacy of ultrasound-guided injections of prolotherapy, platelet-rich plasma (PRP), and corticosteroids on the treatment of RCT based on clinical, functional, and radiological assessment.

Methods

This study was a randomized controlled prospective interventional study which adheres to CONSORT guidelines carried out on 60 patients with RCT selected over a period of 1 year. Inclusion criteria: patients diagnosed clinically with unilateral RCT with symptoms of at least 3 months after failed conservative treatment in the form of physical modalities and therapeutic exercises for at least 4 weeks. Patients were excluded from the study if they had the previous injection in the shoulder within the previous 3 months, history of shoulder trauma, instability, rotator cuff full-thickness tear, shoulder surgery, patients who were suffering from diabetes, rheumatic diseases, chronic liver disease, hematological diseases, tumors, metastatic diseases, their platelet value $< 150,000 \text{ mm}^3$, or on anticoagulation therapy.

All patients were subjected to the following: thorough history taking with especial emphasis on the mechanism of injury, overuse, or spontaneous onset and limited activities. Clinical examination mainly for active and passive range of motion (ROM) flexion, extension, abduction external, and internal rotation using a goniometer. Special Tests as Neer's, Hawkins', and drop arm tests were done. Pain severity was evaluated by visual analog scale (VAS) (0 to 10) where 0 means no pain and 10 indicates the worst pain. Western Ontario Rotator Cuff (WORC) Index: A disease-specific quality of life measurement tool for patients with rotator cuff disease comprised of 21 questions answered on 100-mm VAS items in 5 domains: physical symptoms, sports/recreation, work, lifestyle, and emotions. The total score is from 0 to 2100 as 0 implies no reduction in quality of life and 2100 is the worst score possible. The score can be reported as a percentage of normal by subtracting the total from 2100, dividing by 2100, and multiplying by 100 [8]. Radiological assessment by shoulder plain X-ray to exclude any bone disease or abnormality and diagnostic musculoskeletal ultrasound examination (MSUS) performed using General Electric (GE, Milwaukee, Wisconsin, USA) Logiq P5 R4.0 with a multi-frequency linear transducer probe 3–12 μHz to identify rotator cuff abnormalities as bursitis, tenosynovitis, tendinitis, tendinosis, partial tear (small or large one by measuring its dimensions), or full-thickness tear.

The patients were randomized by closed envelop method divided into three equal groups and each group received 2 ultrasound-guided injections with 2 weeks apart (Fig. 1).

Group 1: Twenty patients were injected with dextrose 25%: 10 ml (8 ml dextrose 25% and 2 ml lidocaine) to all the affected muscles and tendons.

Group 2: Twenty patients were injected with 5 ml PRP: 20 ml of venous blood mixed with 2 ml 10% sodium citrate then centrifuged at 1500 rpm for 15 min to create upper plasma layer, middle buffy coat layer, and a lower red blood cell layer. The upper and middle layers were collected in a sterile empty tube and re-centrifuged at 3500 rpm for 10 min resulting in the formation of a platelet plug and platelet-poor plasma. Platelet-poor plasma was withdrawn and discarded. The remaining PRP and platelet plug resulted in 5 ml PRP with a concentration of 6.7 times of whole blood ready for use [9].

Group 3 (control group): Twenty patients received an injection of 3 ml betamethasone and 2 ml local anesthetic (lidocaine).

Patients were instructed to limit their shoulder movements for 48 h after injection and to use acetaminophen for pain control if needed, but the use of NSAIDs was

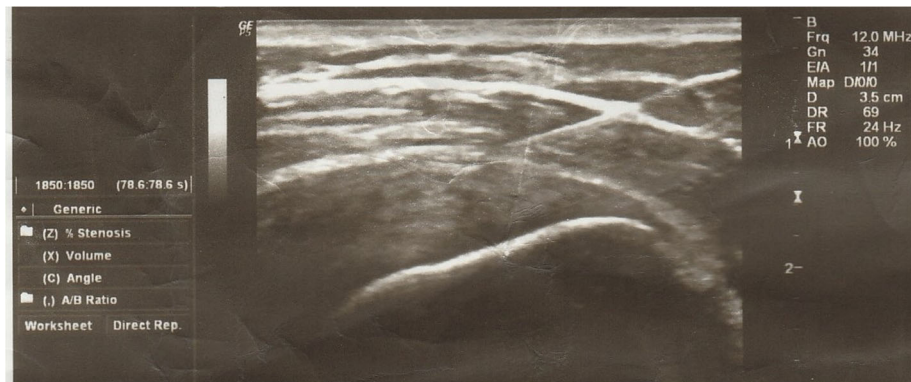


Fig. 1 MSUS image: the image showing the needle while introducing it in the subacromial subdeltoid bursa during injection

prohibited. Reassessment was done after 3 months by shoulder ROM, VAS for pain, WORC index, and diagnostic MSUS examination.

Statistical analysis

Statistical analysis was carried out using the Statistical Package for Social Sciences software version 23. The quantitative data were presented as ranges, and mean \pm standard deviation and qualitative variables were presented as numbers and percentages. Regarding quantitative data, the comparison between paired groups was done by using paired *t* test, between more than two independent groups was done by using one-way ANOVA followed by post hoc analysis using the least significant difference (LSD) test and regarding qualitative data, and comparison between groups was done by using chi-square test and/or Fisher's exact test when the expected count in any cell found less than 5. The confidence interval was set to 95%, and the margin of error accepted was set to 5%. So, the *p* value \leq 0.05 was considered significant. The sample size 60 subjects (20 control on steroid therapy and 20 patients each group) was calculated

by adjusting the power of the test to 80%, and the ratio between cases and controls was set to 2:1.

Results

This study was conducted on 60 patients with RCDs, their mean ages were 43.03 ± 12.17 years, and male to female ratio was 18:42 and dominant hand affection in 57 patients (95%) with 58% of them having occupations involving overhead activities. Regarding MSUS, 35 patients (58.33%) had partial tears, 19 (31.66%) with tendinosis, and 5 (8.33%) with tendinitis, bursitis, and bicipital tenosynovitis were detected in 38 (63.33%) and 24 (40%) of them respectively (Table 1).

Three months post-injection, there was a significant improvement ($p = 0.029$) in ROM of group 1 but no improvement was detected in group 2 or 3 ($p = 0.529$ and 0.121, respectively), with one of the patients in group 2 became worse and had ROM limitations in all directions (Table 2). Also, there was a significant improvement in VAS in group 1 and 3 ($p < 0.001$) but no improvement in group 2 ($p = 0.212$), while there was a significant improvement in all the 3

Table 1 Comparison between the studied groups regarding demographic data

		Dextrose No. = 20	PRP No. = 20	Steroid No. = 20	Test value	<i>p</i> value	Sig.
Age	Mean \pm SD	45.40 \pm 15.56	41.85 \pm 10.21	41.85 \pm 10.21	0.559*	0.575	NS
	Range	18 – 73	18 – 59	18 – 59			
Sex	Females	14 (70.0%)	14 (70.0%)	14 (70.0%)	0.000•	1.000	NS
	Males	6 (30.0%)	6 (30.0%)	6 (30.0%)			
Affected side	Right	12 (60.0%)	12 (60.0%)	12 (60.0%)	0.000•	1.000	NS
	Left	8 (40.0%)	8 (40.0%)	8 (40.0%)			
Occupation	Not working	7 (35.0%)	9 (45.0%)	9 (45.0%)	0.549•	0.760	NS
	Working	13 (65.0%)	11 (55.0%)	11 (55.0%)			
Dominate hand	Right	17 (85.0%)	18 (90.0%)	19 (95.0%)	1.111•	0.574	NS
	Left	3 (15.0%)	2 (10.0%)	1 (5.0%)			

•Chi-square test; *One-way ANOVA, bold values are significant at $p \leq 0.05$

Table 2 Comparison of the 3 groups regarding shoulder joint ROM before and after injections

		Group 1 prolotherapy	Group 2 PRP	Group 3 steroid	t value*	p
Limitation in ROM before injection	No limitation	5 (25.0%)	5 (25.0%)	4 (20.0%)	3.522	0.741
	One direction	1 (5.0%)	5 (25.0%)	4 (20.0%)		
	Two direction	5 (25.0%)	4 (20.0%)	5 (25.0%)		
	All directions	9 (45.0%)	6 (30.0%)	7 (35.0%)		
Limitation in ROM after injection	No limitation	15 (75.0%)	5 (25.0%)	7 (35.0%)	21.517	0.001
	One direction	1 (5.0%)	7 (35.0%)	6 (30.0%)		
	Two direction	2 (10.0%)	1 (5.0%)	6 (30.0%)		
	All directions	2 (10.0%)	7 (35.0%)	1 (5.0%)		
<i>p</i> value between before and after injection*		0.029	0.529	0.121		

*Chi-square test, bold values are significant at $p \leq 0.05$, ROM range of motion, PRP platelet-rich plasma

groups regarding WORC index ($p < 0.001$, 0.049, and $p < 0.001$, respectively) (Table 3).

Regarding ultrasound findings post-injection, there was a significant improvement in groups 1 and 2 ($p < 0.001$ and $p = 0.020$, respectively) in the grade of tendon lesions but no improvement occurred in group 3 ($p = 0.470$) with a significant difference ($p < 0.000$) between the 3 groups. Bursitis improved significantly in groups 1 and 3 ($p < 0.001$ and $p = 0.025$, respectively), and no improvement was noticed in group 2 ($p = 1.000$). Also, bicipital tenosynovitis was improved in group 3 ($p = 0.028$) while no improvement was detected in groups 1 or 2 ($p = 0.113$ and 0.465, respectively) (Table 4). On comparing all the 3 groups to each other, post injection group 1 showed better results than groups 2 and 3 (Table 5, Figs. 2 and 3).

Discussion

In the current study, we compared ultrasound-guided injections of prolotherapy, corticosteroid, and PRP for the treatment of RCT.

We observed that group 1 patients achieved significant improvements ($p = 0.029$) in ROM and ($p < 0.001$) in other parameters used after prolotherapy injection. This agreed with Lee et al. [10], Seven et al. [5], and Huang [11] and Soliman et al. [12], which could be explained as

hypertonic dextrose injection initiates a brief inflammatory cascade which in turn stimulates natural healing process with subsequent clinical improvement following the restoration of tissue integrity.

Also, by stimulating the production of multiple pro-fibroblastic cytokines and glucose transport into human cells by glucose transporter (GLUT1) which is coupled with cytokine elevations and a direct pain-modulating effect either by downregulation of the transient receptor potential vanilloid type 1 (TRPV1) receptor, a chief receptor in maintenance of a chronic pain state, or by the effects on downstream mediators of TRPV1 activation [13].

Among group 2 patients, significant ($p = 0.049$ and $p = 0.020$) improvement of WORC index and tendon lesions, respectively, with no improvements noticed regarding other parameters used. This may be related to the beneficial effects of PRP on the healing process attributed to bone morphogenetic proteins, TGFs and FGFs [14], which proved to promote tendon cell proliferation, collagen synthesis, and vascularization in vitro and in vivo [15]. This agreed with Kesikburun and his colleague [1] and Carr et al. [16] who state that no difference in clinical outcomes in patients who received PRP injection for RCT compared to controls. Also, our results were in accordance with Rha et al. [17] who

Table 3 Comparison of the 3 groups regarding VAS and WORC index before and after injections

		Group 1 Prolotherapy No. = 20	Group 2 PRP No. = 20	Group 3 Steroid No. = 20	t value*	p
VAS before	Mean \pm SD Range	8.30 \pm 1.38 (6–10)	7.15 \pm 1.50 (5–10)	7.65 \pm 2.50 (6–10)	1.917	0.156
VAS after	Mean \pm SD Range	2.20 \pm 2.78 (0–8)	6.65 \pm 2.41 (3–10)	4.90 \pm 1.92 (1–7)	17.492	0.000
<i>p</i> value		< 0.001	0.212	< 0.001		
WORC before	Mean \pm SD Range	23.72% \pm 21.25% (4–66.5%)	25.75% \pm 13.12% (5%–50%)	24.83% \pm 15.13% (7%–55%)	0.073	0.930
WORC after	Mean \pm SD Range	80.35% \pm 31.49% (10%–100%)	33.90% \pm 23.99% (5%–80%)	51.75% \pm 23.58% (20–95%)	15.519	0.000
<i>p</i> value		< 0.001	0.049	< 0.001		

*One-way ANOVA, bold values are significant at $p \leq 0.05$, VAS visual analog scale, WORC Western Ontario Rotator Cuff Index, PRP platelet-rich plasma

Table 4 comparison of the 3 groups regarding MSUS findings before and after injections

		Group 1 Prolotherapy	Group 2 PRP	Group 3 Steroid	t value*	p
MSUS (pre-intervention)	N.	0 (0.0%)	0 (0.0%)	0 (0.0%)	4.764	0.574
	tendinitis	2 (10.0%)	1 (5.0%)	3 (15.0%)		
	tendinosis	7 (35.0%)	5 (25.0%)	7 (35.0%)		
	Partial tear	11 (55.0%)	14 (70.0%)	10 (50.0%)		
MSUS (post intervention)	N	12 (60.0%)	0 (0.0%)	2 (10.0%)	29.649	0.000
	tendinitis	1 (5.0%)	8 (40.0%)	4 (20.0%)		
	tendinosis	6 (30.0%)	5 (25.0%)	5 (25.0%)		
	Partial tear	1 (5.0%)	7 (35.0%)	9 (45.0%)		
<i>p</i> value between before and after*		0.001	0.020	0.470		
MSUS before(bursitis)	No	8 (40.0%)	6 (30.0%)	8 (40.0%)	0.574	0.750
	Yes	12 (60.0%)	14 (70.0%)	12 (60.0%)		
MSUS after (bursitis)	No	18 (90.0%)	6 (30.0%)	15 (75.0%)	17.143	0.000
	Yes	2 (10.0%)	14 (70.0%)	5 (25.0%)		
<i>p</i> value between before and after*		0.001	1.000	0.025		
MSUS before (bicipital tenosynovitis)	No	14 (70.0%)	14 (70.0%)	12 (60.0%)	0.600	0.740
	Yes	6 (30.0%)	6 (30.0%)	8 (40.0%)		
MSUS after (bicipital tenosynovitis)	No	18 (90.0%)	16 (80.0%)	18 (90.0%)	1.154	0.562
	Yes	2 (10.0%)	4 (20.0%)	2 (10.0%)		
<i>p</i> value between before and after*		0.113	0.465	0.028		

*Chi-square test, bold values are significant at $p \leq 0.05$; MSUS musculoskeletal ultrasound, PRP platelet-rich plasma, N normal echogenicity

reported PRP injections revealed no improvement of shoulder ROM although provided more significant pain relief and improved arm function in patients with RCT or partial tear when compared to dry needling.

Our findings were contrary to Shams et al. [18] who demonstrated a statistically significant improvement in clinical outcomes 12 weeks after PRP injections but no difference after 24 weeks. Also, Ibrahim et al. [19] revealed a significant improvement in VAS, shoulder ROM, tear, and effusion but no improvement in tendinitis or bursitis 8 weeks after PRP injections.

A meta-analysis of PRP effect on surgical repair of rotator cuff tears by Warth et al. [20] indicated that there were no differences in clinical outcomes between patients who received PRP and those who did not, but it significantly lower the increased incidence of re-tear rates for large (> 3 cm) tear. However, Vavken et al. [21] found that PRP is effective in reducing re-tear rates in the arthroscopic repair of small- and medium-sized rotator cuff tears but no evidence that re-tear rates decreased for large and massive tears.

This could be explained by the substantial variability in the methods of PRP production among commercial systems [22]. Additionally, within a given PRP preparation protocol, there is a high degree of inter- and intra-subject variability in the PRP composition [23] which makes it difficult to assess the efficacy of PRP treatment for rotator cuff disease.

In group 3 in this study, there was a significant ($p < 0.001$, $p < 0.001$, $p = 0.025$, and $p = 0.028$) improvement of VAS, WORC index, bursitis, and bicipital tenosynovitis, respectively, but no improvement in shoulder ROM or tendon lesion.

Our findings were similar to Shams et al. [18] where there was an improvement of VAS, but MRI showed a slight nonsignificant improvement in the grades of tendinopathy/tear. Although, Ibrahim et al. [19] revealed that there was a significant improvement of pain and bursitis as our results, yet Shoulder Disability Questionnaire, ROM, and tendinitis were improved in contrary to ours. This could be explained by the analgesic effects of corticosteroid which may be mediated by neuropeptides,

Table 5 Comparison between the 3 groups after injection

	P1 (prolotherapy versus PRP)	P2 (prolotherapy versus steroid)	P3 (PRP versus steroid)
VAS after	0.000	0.001	0.025
ROM after	0.005	0.031	0.037
MSUS after (bursitis)	0.000	0.211	0.004
MSUS after (tendon lesion)	0.000	0.001	0.310

Post hoc analysis using LSD test, bold values are significant at $p \leq 0.05$; VAS visual analog scale, ROM range of motion, MSUS musculoskeletal ultrasound, PRP platelet-rich plasma

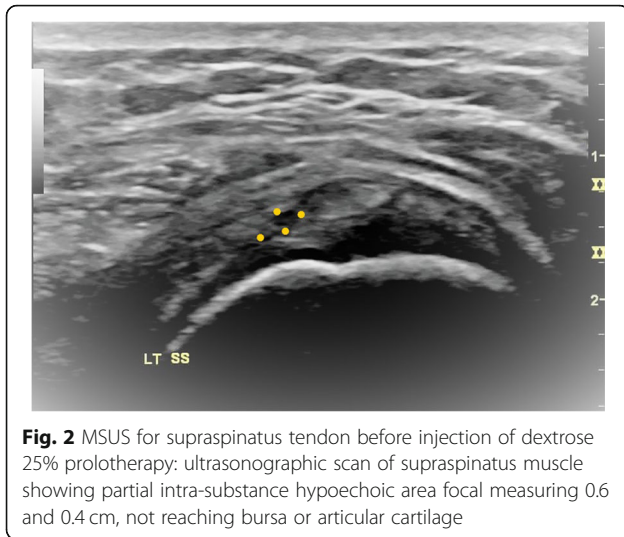


Fig. 2 MSUS for supraspinatus tendon before injection of dextrose 25% prolotherapy: ultrasonographic scan of supraspinatus muscle showing partial intra-substance hypoechoic area focal measuring 0.6 and 0.4 cm, not reaching bursa or articular cartilage

calcitonin gene-related peptide, and substance P which are found to increase in tendinopathies [24]. However, this should be balanced by their deleterious effects on the tendon tissue as collagen disorganization, decreased mechanical properties of the tendon, and long-term harm to the tendon tissue and cells [25].

In the present study, on comparing the dextrose prolotherapy to PRP versus steroid injection, we found significant results for the healing of tendon injuries for both dextrose prolotherapy and PRP, leading to decrease tear size up to complete healing for tendinosis and small partial tears which is due to their regenerative power, while non-significant change for steroid group. But for the effect on bursitis and tenosynovitis leading to improvement in pain, ROM, VAS, and WORC index, only prolotherapy having a significant effect which may be due to anti-inflammatory effect and pain modulation effect in addition to its regenerative power and to some extent steroids due to its anti-inflammatory effect.

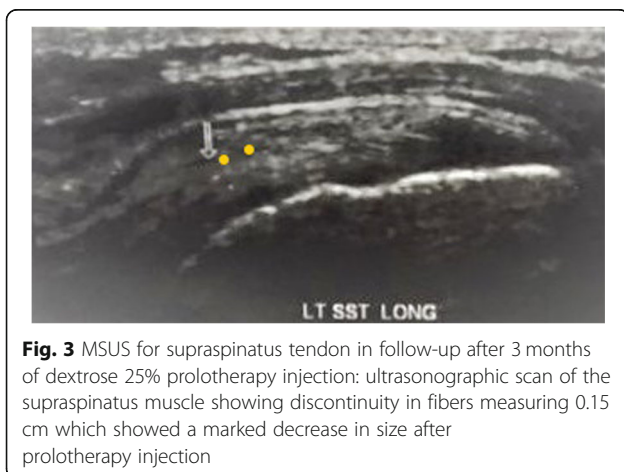


Fig. 3 MSUS for supraspinatus tendon in follow-up after 3 months of dextrose 25% prolotherapy injection: ultrasonographic scan of the supraspinatus muscle showing discontinuity in fibers measuring 0.15 cm which showed a marked decrease in size after prolotherapy injection

Also, there was no side effects or difficulties related to prolotherapy injection except for pain with needle insertion, the same with PRP, but in addition to the extra cost added, while steroid has its usual side effects of the small amount released to bloodstream (as a transient increase in blood pressure or blood sugar) which was not significant in our study as we excluded diabetic and hypertensive patients.

The limitations in our study were the small sample size and the short term of follow-up period to demonstrate how long the effect will be maintained.

Conclusion

Prolotherapy injections improve shoulder ROM, VAS, WORC index, and rotator cuff tendon healing while PRP injections improve WORC index and tendon healing, but steroid injection has no effect on healing. Prolotherapy injection was superior to PRP and steroid in the treatment of RCT.

Abbreviations

RCT: Rotator cuff tendinopathy; RCDs: Rotator cuff diseases; PRP: Platelet-rich plasma; ROM: Range of motion; VAS: Visual analog scale; WORC: Western Ontario Rotator Cuff Index; MSUS: Musculoskeletal ultrasound; ml: Milliliter; NSAIDs: Non-steroidal anti-inflammatory drugs; FGF2: Fibroblast growth factor; TGF: Transforming growth factor β ; LSD: Least significant difference; TRPV1: Transient receptor potential vanilloid type 1 receptor

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Authors' contributions

HMAS: Contribution to the conception and design of the work; the acquisition, analysis, and interpretation of data; and revision through a suggestion of the research idea and aim, clinical assessment of patients and controls, and preparation of the manuscript and statistical data. He also approved the submitted version and agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work. MAN: Contribution to the design of the work; follow-up of patients, interpretation of data; and has drafted the work and substantively revised it. He also contributed to the preparation of the manuscript and statistical data, approved the submitted version, and agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work. The authors have read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Ain Shams University, Faculty of Medicine Research Ethics Committee (REC) FWA 000017s8s. FMASU R41/2018. A written informed consent was obtained from patients sharing in the study.

Consent for publication

A written consent was taken from the patients and available upon request.

Competing interests

The authors declare that they have no competing interests.

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