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Research Article

# Partial Rotator Cuff Tear outcome between prolotherapy with physical rehabilitation compared to physical rehabilitation only: A Meta-analysis approach

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## ABSTRACT

Partial Tear Rotator Cuff Tendinopathy (PTRCT) impacts 15% to 50% of the population and increases in prevalence with individuals' age. Several first-line management strategies for treating rotator cuff disease, such as physical rehabilitation and/or injection, have been reported. However, optimum management is debatable. This study aims to explore the outcome management combination of prolotherapy and physical rehabilitation with physical rehabilitation only for PTRCT. Randomized Control Trial (RCT) studies From PubMed, Cochrane Library, ScienceDirect, ProQuest, And Google Scholar were included. Two independent reviewers evaluated the quality of RCTs using the Cochrane Risk of Bias Tool. The primary result was pain reduction, with functional improvement as a secondary outcome. Meta-analysis was performed using Review Manager 5.4 software. Our meta-analysis included 5 RCT studies involving 263 patients. Standardized mean difference (SMD) was collected from all of the studies. In this study, pain reduction was significantly decreased in the prolotherapy group compared with physical rehabilitation only during 12 weeks follow-up (-0.97 (95% -1.63 to -0.31) with p: 0.0004) and obtained $I^2$ 57 % that, representing moderate heterogeneity. In contrast, Functional improvement did not significantly reduce (-1.04 (95% -5.45 to 3.317) with p: 0.64. In conclusion, Prolotherapy with physical rehabilitation can reduce pain in long-term (12 weeks) patients with PTRCT compared to physical rehabilitation only but give no significant effect in improving functional outcomes.

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## INTRODUCTION

Rotator cuff tendinopathy is one of the most frequent musculoskeletal disorders and the most common shoulder illness, impacting 15% to 50% of the population and increasing in prevalence with individuals' age (Catapano et al., 2020). Rotator cuff tears are estimated to affect at least 10% of people over 60(Ryösä et al., 2016). Rotator cuffs can be partial and total tears, especially In Partial-thickness rotator cuff tears (PTRCT), commonly associated with Shoulder stiffness, pain, and limited range of motion (Park et al., 2020). Shoulder stiffness can affect decreased health-related quality of life, increased absences from work, and increased healthcare resource consumption (Smith et al., 2000). It is a significant clinical issue for clinicians due to the wide variety of pathologies that it can present, from tendinosis to calcific tendonitis, partial- and full-thickness tears to large and massive irreparable rotator cuff tears affecting any combination of the four-rotator cuff muscle and tendons (Rashid et al., 2017; Sambandam et al., 2015; Schmidt et al., 2015). In some cases, the prevalence incidence of PTRCT is estimated at 4% at age 40, 26% at age >60, and 20% in otherwise asymptomatic populations (de Sanctis et al., 2020).

Several management strategies for rotator cuff disease have been reported, including conservative and surgical. This management depends on the Patient's age, activity level, symptoms, degree of impairment, physical examination, and imaging findings (K. M. Lin et al., 2018). However, the optimal treatment for PTRCT remains debatable (Min et al., 2013). In a previous systematic review, Corticosteroids are effective in the short term (3-6 weeks) but not in the long term (over 24 weeks), decreasing pain and improving function. In contrast, PRP and Prolotherapy may produce better long-term results (over 24wk) (M. T. Lin et al., 2019).

The injection method and conservative treatment, such as physical rehabilitation, provide a satisfactory outcome for a patient with PTRCT. Conservative treatment options include lifestyle modifications and physical therapy. In recent years, various systematic reviews have proven the efficacy of physiotherapy and strengthening muscle activities in treating rotator cuff disorders (Desjardins-Charbonneau et al., 2015; Kuhn, 2009). Exercise is a broad concept that combines the following interventions: range of motion exercises, stretching and flexibility exercises, and strengthening exercises with manual therapy with several injections can give promising outcomes. Nevertheless, prolotherapy is required since existing physical exercise has not produced the desired results (Ainsworth & Lewis, 2007; Bang & Deyle, 2000). Therefore, this systematic review aims to explore the outcome management combination of prolotherapy and physical rehabilitation with physical rehabilitation only for PTRCT.

## METHODS

### Data sources and searches

Published articles were selected from five databases [PubMed, Cochrane Library, ScienceDirect, ProQuest, and Google Scholar]. The search was carried out until February 2022. The keywords used in the search were (Rotator cuff tear or Rotator cuff injuries) AND (Prolotherapy or Proliferation therapy) OR (Dextrose) according to MeSH Terms. Next, we move it to Mendeley for reference settings and remove duplicate findings. The search was limited to English language articles, limited in ten past years, and did not include grey literature in this study. All methods in this study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses (PRISMA) (Hutton et al., 2015). PRISMA Diagram shown in Figure 1.

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**Eligibility Criteria**

*Type of studies*

The criteria used initially in article selection through automation tools were full articles and limited in ten past years. Article selection was carried out based on inclusion and exclusion criteria. We included all published RCTs. We excluded research including quasi-experimental trials, observational studies, case series, single-arm studies, and animal studies. The article included a study that completed the following inclusion criteria: Adults patients with age > 18 years old with partial rotator cuff who underwent Prolotherapy intervention only; the outcome results represent pain and a function score. Whereas patients with a partial rotator cuff that performed injection more than one type of technique, full-thickness tears, rheumatological disease, and underwent surgery on the shoulder were excluded from this study. All search results were written using Microsoft Excel and then duplicated studies were eliminated using Mendeley.

*Participants*

We selected studies wherein patients diagnosed with rotator cuff tendinopathy either clinical or imaging examination.

*Intervention*

Allocated groups in studies treated with only one type of injection therapy (Prolotherapy) were eligible for inclusion. There were no restrictions on the number of prolotherapy injections or the administration technique.

*Outcome*

In this study, pain reduction is used as a primary outcome. However, functional improvement is used as a secondary outcome. Pain reduction is measured using a visual analog scale (VAS). Then, all types of established shoulder function and pain measurements were acceptable for functional outcomes. Time points for postinterventional follow-up were assigned more than three weeks.

**Data extraction**

Data obtained from each study are the characteristics of the study and outcomes. For the characteristics, subjects' data were collected, such as the type of study, number of samples, age, follow-up time, the dose used in prolotherapy, and following adverse effects. Especially the sample study was written as either a control group or intervention group, followed until the end of the study. The recorded outcomes are prioritized on the pain score and function score. Then, all types of established shoulder function and pain scoring systems were acceptable for the Function score. Mean, SD and significance values were also recorded specifically according to the method for outcome measurement. Other outcomes are additional.

**Quality Assessment**

We used two types of tools to evaluate the risk of bias: the Cochrane Risk of Bias Tool (RoB) and the JADAD score. The Cochrane Risk of Bias Tool was used to assess the quality of RCTs, as detailed in the Cochrane Handbook for Systematic Reviews of Interventions. There are five main categories of bias. The outcome was assessed as low, unclear, and high risk. Each item was evaluated independently by two authors. The disputes were resolved by consensus with the corresponding author. The consensus was used to resolve any disagreement.

**Data Synthesis and Analysis**

The meta-analysis was performed using Windows Review Manager (RevMan) version 5.4.1. Continuous variables are presented as mean and standard deviation (SD) with confidence intervals of 95 percent (CI). P-values

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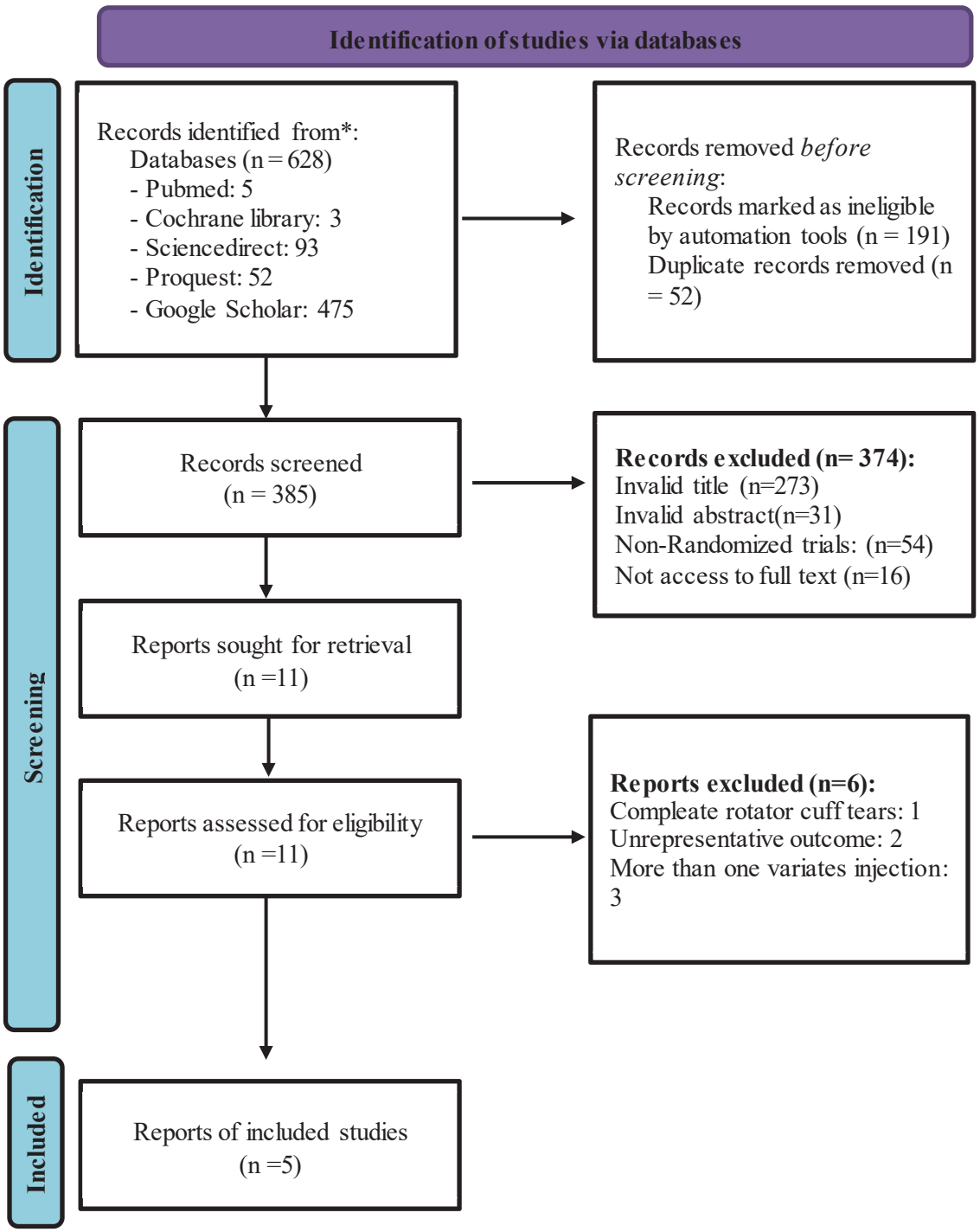


**Figure 1.** A Flow Diagram of the Study using PRISMA

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less than 0.05 were considered statistically significant. A meta-analysis determined whether at least two studies examined the same variables and whether a random or fixed effect based on heterogeneity was obtained.

## RESULTS

### Characteristics of Studies and Demographics

From the initial article search, we obtained 628 journal articles, five from PubMed, three from Cochrane Library, 93 from Science Direct, 52 from ProQuest, and 475 from Google Scholar respectively. A total of 191 articles were removed with automation tools in each database due to full-text review only and English language, and 52 studies were duplicated. Lastly, A total of 385 articles were screened. Following the relevance of titles and abstracts, there were 374 studies excluded because of not being matched with the study, not randomization trial, and cannot access the full text. The discrepancy between abstracts and titles is based on research criteria, especially patients, interventions, objectives, and research methods. Therefore, only 11 studies can proceed to the next stage. According to inclusion and exclusion criteria, we are leaving five articles to include for analysis. All included studies only were designed for randomized controlled trials.

The included studies contained a total of 263 individuals with rotator cuff tendinopathy. Their sample sizes ranged from 5 to 44 participants for the control group and 7 to 57 participants for the experimental group. By comparing research, the mean age of participants ranged between 46 to 58 years old in the control group and 46.2 to 60 years old in the experimental group. The follow-up in some studies varied from 3, 12, until 36 weeks. Two studies performed injections with two repetitions (Bertrand et al., 2016; Seven et al., 2017), while the others only underwent a one-time repetition dextrose injection. All studies have the same injectable substance, generally dextrose, but there are variations in dosage in several studies in the experimental group. In the control group, all studies used either normal saline or physiotherapy only. There are two studies there are only two studies comparing physiotherapy without using a normal saline injection in the control group (George et al., 2018; Kazempour Mofrad et al., 2021).

### Risk of bias assessment

The risk of bias summary and graph is shown in figure 2 and 3. All studies have a low risk of bias in random sequencing because all of the studies use appropriate randomization techniques. Then only one study explained the concealing processes in detail, whereas two did not explicitly confirm the concealment methods, and two showed no allocation concealment. Two studies have a low risk of blinding participants and stated clearly, and two studies have a high risk of blinding bias due to nonblinding between participants and investigators. George et al. and Kazempour et al. have a high risk of blinding outcome assessment because the researchers do their assessment.

Other studies have a low risk of blinding outcomes due to applying an acceptable randomization strategy to assess the outcome. Furthermore, George et al. indicated a high risk of selective reporting bias due to incomplete reporting of baseline demographics, outcomes, and standard deviations (SDs). In contrast, most studies demonstrated an unclear risk of selective reporting due to the absence of a published study protocol. Then, George et al. and Seven et al. were categorized as having a high risk of incomplete outcome data bias due to a significant loss to follow-up rate in the control group. Two studies have a high risk of bias. They can be a confounding factor because

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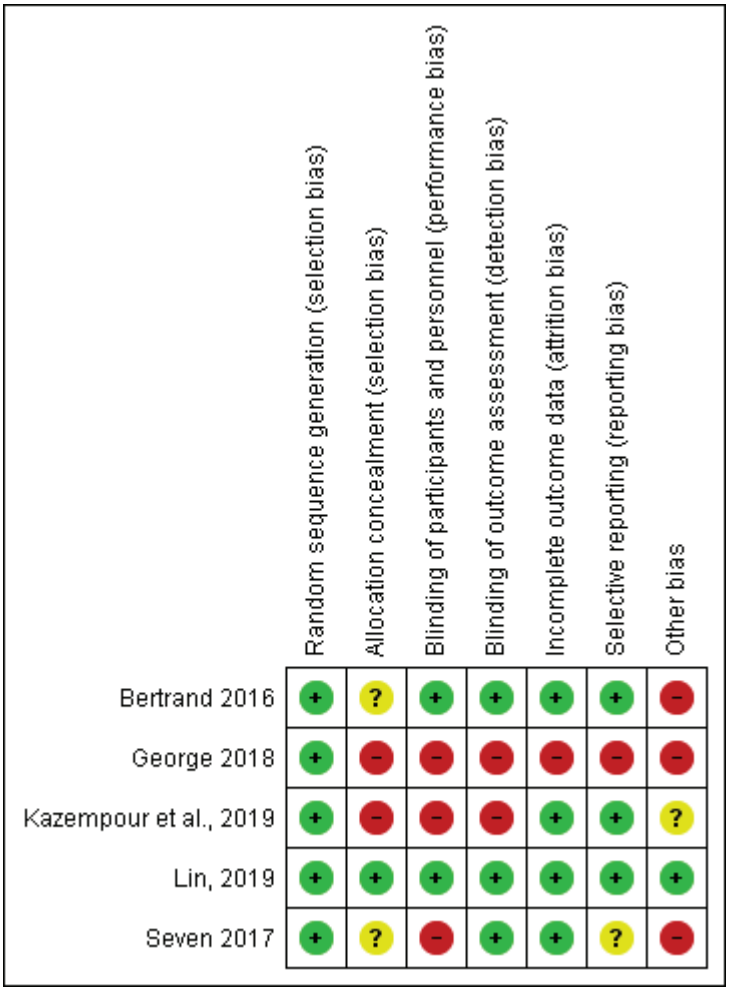


**Figure 2.** Risk of Bias Summary

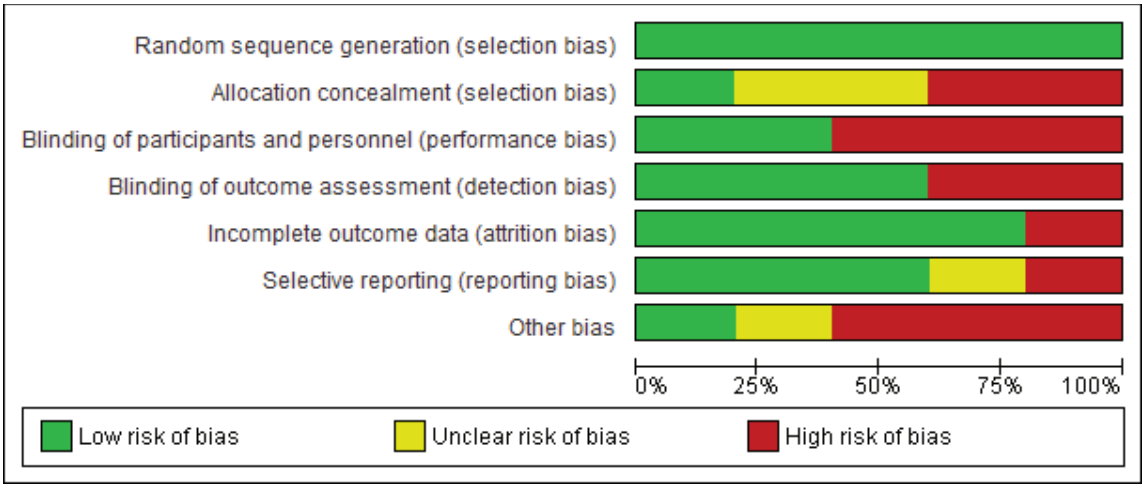


**Figure 3.** Risk of Bias Graph

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of two injections that will affect the primary outcome and one study with high risk because it was an open-label study, so it was non-blinding between the researcher and participants.

**Included Studies**

Bertrand et al. (2016) performed a double-blind, randomized, controlled experiment with 73 patients with chronic, moderate to severe shoulder pain symptoms for more than three months that were confirmed by ultrasound. The participants were randomly categorized into three groups: (1) the Enth-Dex Group is injected using 25% dextrose/0.1% lidocaine/saline onto painful entheses, then (2) the Enth-Saline group is injected using 0.1% lidocaine/saline onto painful entheses, and last (3) Superfic-Saline group is injection 0.1% lidocaine/saline superficial to painful entheses with depth 0.5- to 1-cm. All of the participants were assessed at baseline, 12 weeks (3mo), and 36 weeks (9mo) after injection for improvement in symptom severity using a visual analog scale (VAS) and also evaluated tendon rotator cuff structure using Ultrasound Shoulder Pathology Rating Scale. Patients underwent follow-up interventions one and two months after the initial intervention. Only one Patient in the enthesis saline group was lost to follow-up due to the development of adhesive capsulitis during the therapy period. After three months, pain intensity was reduced by 3.0±0.5, 2.7±0.7, and 2.7±0.6 in the enthesis dextrose, enthesis saline, and superficial saline groups, respectively. The difference between the enthesis dextrose and superficial saline groups was statistically significant, but not between the enthesis dextrose and enthesis saline groups (Bertrand et al., 2016).

Seven et al. (2017) published an open-label randomized controlled trial on 120 participants that compared Ultrasound-guided enthesis injections around the shoulder with physiotherapy and exercise programs. Enthesis injection using Ultrasound-guided contains 4 mL of 25% dextrose plus up to 20 mL of 15% dextrose, depending on the injection location. All participants were allowed repeat injections for a maximum of six treatments, discontinued if the pain was reduced by more than 75% or when the participant decided out of repeat injections. All participants were asked to describe their pain intensity on a VAS scale, their function on the Western Ontario Rotator Cuff Index (WORC) and the Shoulder Pain and Disability Index (SPADI), and their active range of motion by an outcome assessor who was blind to patient allocation. All the outcome was observed at baseline, three, six, and twelve weeks after intervention. Nineteen patients were lost to follow-up, sixteen in the control group and three in the prolotherapy group, due to adverse events, dissatisfaction, or insufficient data. Prolotherapy patients showed statistically significant improvements in pain intensity on a VAS scale, function assessed by the WORC and SPADI, and internal rotation, abduction, and flexion range of motion compared to control groups (Seven et al., 2017).

George et al. (2018) conducted a one-time open-label randomized controlled trial on twelve participants. This study aims to compare the efficacy between injection of 0.5% lidocaine and 0.5-10 mL of 12.5% dextrose into a central point of supraspinatus tendinosis with conventional physiotherapy in patients with focal supraspinatus tendinosis. Based on the ultrasound guide, Patients with total tears were excluded from this study. All patients underwent the same amount of physiotherapy. Twelve participants were randomly assigned to prolotherapy or physiotherapy using a random-digit analyzer. After injection, evaluation was performed at baseline and 12 weeks later. Functional assessment of all Patient's symptoms was validated using a questionnaire on Disabilities

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of the Arm, Shoulder, and Hand (DASH) and confirmed by ultrasound evaluations. There was a significant improvement in abduction active range of motion in the prolotherapy group compared to the physiotherapy group. In contrast, forward flexion, extension, internal rotation, and external rotation showed no significant difference between groups. Additionally, while both groups improved from baseline to the 12-week follow-up, there was no significant difference in mean DASH function score, pain score, or ultrasonography features at the 12-week follow-up (George et al., 2018).

Lin et al. (2019) did a double-blind, randomized controlled experiment comparing a single-site ultrasound-guided injection of 20% dextrose with 5% normal saline injection into the supraspinatus enthesis. In neither group was concurrent exercise intervention controlled for or reported. Thirty-one patients were selected randomly, and all assigned patients received the appropriate intervention. No patients were lost to follow-up. All patients had their pain intensity assessed using the VAS, their function assessed using the SPADI, and their range-of-motion and supraspinatus ultrasound characteristics, including thickness and echogenicity, measured at baseline, two- and six-weeks post-intervention. There was no significant difference in any measurable outcome between groups or between patients and controls at the 6-week follow-up (C. L. Lin et al., 2019).

**Meta-analysis result**

**Change in pain level**

Metanalyses were performed to determine whether there are any differences between prolotherapy injection and physical rehabilitation of patients with PRTC tears. We entered the VAS pain score mean and Standard deviation value at 12 weeks of follow-up. Our meta-analysis for pain reduction was performed to know from our meta-analysis test result that the heterogeneity is 57 %, representing moderate heterogeneity. The pooled random-effects raw mean difference was -0.97 (95% -1.63 to -0.31) points with p: 0.0004.

**Change in Functional Outcome**

The functional outcome was assessed only by SPADI score at 2-3 months of the follow-up period. Our meta-analysis for pain reduction was performed based on our meta-analysis test result. The heterogeneity is 92%, representing high heterogeneity. The pooled random-effects raw mean difference was -1.04 (95% -5.45 to 3.317) points with a test for overall effect Z = p: 0.64.

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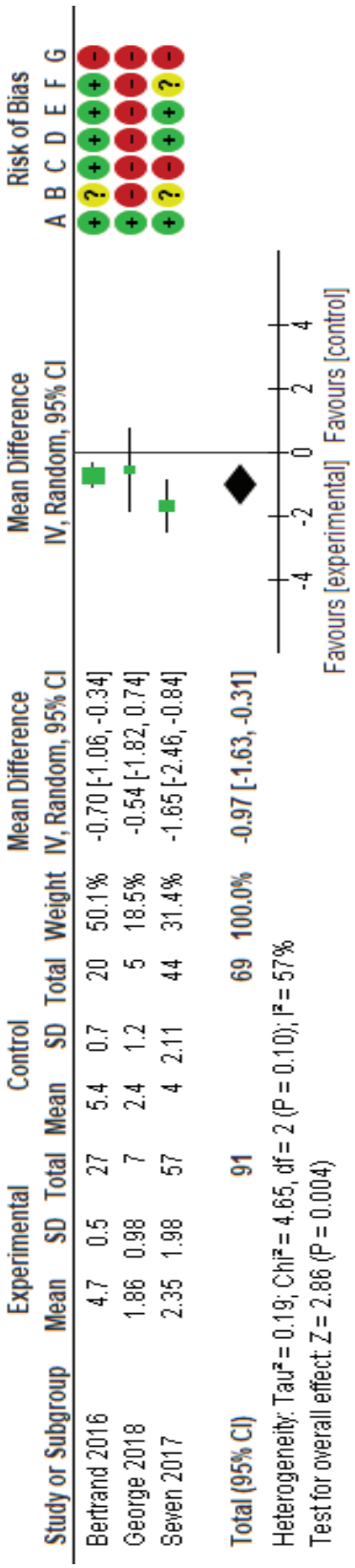


**Figure 4.** Forest plot of pain reduction in 12 weeks follow up

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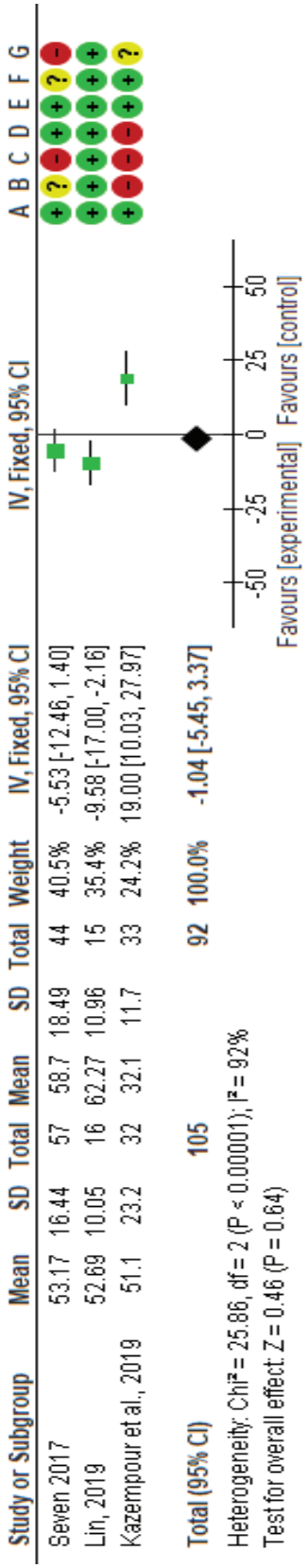


**Figure 5.** Forest plot of functional outcome using SPADI scale in 2-3 weeks of follow up

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| No | Author, year | Study | Inclusion Criteria | Interventions | Dose | Control | Total Sample | | Age (Ctrl/Expe) | Outcome | | | Follow Up (weeks) | Adverse Effect |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Control | Sample | | Pain Score (12 wk) | Function Score (12 wk) | | | |
| 1 | Bertrand, 2016 | RCT/ Level 1 | Supraspinatus pathology with >3 mo of symptoms. Pathologes consisted of non-calcific or calcific tendinosis, a partial tear or full thickness tear less than 1.2 cm, as noted on high-resolution ultrasound. | Prolotherapy Injection (0,1,2 mo) | Prolotherapy: Dextrose 25 %/ Lidocaine 0,1% Placebo: Lidocaine 0,1%/ Saline and Physical rehabilitation | Saline and Physical rehabilitation | 27 | 27 | 53.8/51.1 | VAS: Intervention - Baseline: 7.7 ± 1.7 - Reduction: 3.0 ± 0.5 Control - Baseline: 8.1 ± 2.7 - Reduction: 2.7 ± 0.7 | Ultrasound Shoulder Pathology Rating Scale: Intervention - Baseline: 4.0 ± 0.4 - Reduction: 3.7 ± 0.5 Control - Baseline: 4.3 ± 0.4 - Reduction: 3.7 ± 0.4 | 12, 36 | None |
| 2 | Seven et al., 2017 | RCT/ Level 1 | Rotator cuff lesions with >6 mo of symptoms. Pathologies consisted of tendinosis or partial tear of any rotator cuff tendons diagnosed by MRI. | Prolotherapy Injection | Prolotherapy: Dextrose 15 %/ Lidocaine and physiotherapy | physiotherapy | 44 | 57 | 46.31/50.19 | VAS: Intervention - Baseline: 7.85 ± 1.29 - Reduction: 2.35 ± 1.98 Control - Baseline: 7.36 ± 1.38 - Reduction: 4.00 ± 2.11 | SPADI Intervention - Baseline: 74.76 ± 18.54 - Reduction: 16.12 ± 12.82 Control - Baseline: 68.62 ± 20.4 | 3,6,12 | | |

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| | | | | | | | | | | | | | |
| | | | | | | | | | | | | 12 | |
| | | | | | | | | | | | | DASH: Intervention - Baseline: 60.14 ± SD - Reduction: 43.89 ± SD Control - Baseline: 56.86 ± SD - Reduction: 46.68 ± SD | - Reduction: 37.25 ± 20.32 |
| | | | | | | | | | | | | VAS: Intervention - Baseline: 3.29 ± SD - Reduction: 1.86 ± SD Control - Baseline:3.2± SD - Reduction: 2.4 ± SD | |
| | | | | | | | | | | | | 7 | |
| | | | | | | | | | | | | 5 | |
| | | | | | | | | | | | | 58/60 | |
| | | | | | | | | | | | | Physical rehabilitation | |
| | | | | | | | | | | | | Placebo: Lidocaine 0,1%/ Saline and Physical rehabilitation e | |
| | | | | | | | | | | | | Prolotherapy Injection | |
| | | | | | | | | | | | | Rotator cuff lesions with >6 mo of symptoms. Pathologies consisted of tendinosis or partial tear of any rotator cuff tendons diagnosed by MRI. | |
| | | | | | | | | | | | | RCT/ Level 1 | |
| | | | | | | | | | | | | George et al., 2018 | |
| | | | | | | | | | | | | 3 | |

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| 4 | Kazempour et al., 2019 | RCT/ Level 1 | Small rotator cuff tear or tendinopathy more than 3 months on a magnetic resonance imaging | Dextrose Prolotherapy | Prolotherapy: Dextrose 12,5 %/ Lidocaine 2% And Physiotherapy | Physiotherapy | 56.9/52.5 | 33 | 32 | not mentioned in article | SPADI Intervention - Baseline: 31.1 ± 23.3 - Reduction: 47.3 ± 19.8 Control - Baseline: 32.1 ± 11.7 - Reduction: 28.5 ± 8.2 | 2, 12 | None |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 | Lin, 2019 | RCT/ Level 1 | Chronic rotator cuff lesions with >6 mo of symptoms. Pathologies consisted of chronic supraspinatus tendinopathy including tear or tendinosis diagnosed using ultrasound. Full thickness tears or calcific tendinopathy was not excluded | Prolotherapy Injection | Prolotherapy: Dextrose 20 % and Physical rehabilitation | Normal Saline - Physical rehabilitation | 48./46.2 | 15 | 16 | VAS: Intervention - Baseline: 5.56 ± 0.81 - Reduction: 5.13 ± 0.72 Control - Baseline:5.33 ± 0.82 - Reduction: 4.87 ± 0.64 | SPADI Intervention - Baseline: 60.50 ± 7.87 - Reduction: 61.56 ± 4.68 Control - Baseline: 65.00 ± 2.78 - Reduction: 60.00 ± 4.90 | 3, 6 | None |

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## DISCUSSION

Management strategies for rotator cuff disease remain debatable. Oral nonsteroidal anti-inflammatory medications (NSAIDs) and several injections are favorable as the first-line therapy method for PTRCT. Moreover, surgical intervention is often indicated after three to six months of conservative treatment failure or in younger patients with severe tears (K. M. Lin et al., 2018b; Matthewson et al., 2015). The various injection for the rotator cuff that can be used encompass corticosteroids, platelet-rich plasma (PRP), Prolotherapy (hypertonic dextrose), hyaluronic acid (HA), and Botulinum toxin (BTX) (Bertrand et al., 2016; Chou et al., 2010; Hauser et al., 2016; Hong et al., 2011; Kesikburun et al., 2013; Kim et al., 2012; Min et al., 2013; Penning et al., 2012; Sari & Eroglu, 2020).

In this study, outcome assessment measures pain and functional outcome between prolotherapy and physical rehabilitation. However, not all studies performed a meta-analysis. The researcher decided to conduct a meta-analysis study based on the similarity of the method and follow-up period after injecting prolotherapy that eligible has performed a meta-analysis. In pain assessment outcome, only three studies matched the acceptable criteria, using either a visual analog scale or a 12-week follow-up period. Our meta-analysis test showed that prolotherapy's effect significantly reduces pain in the prolotherapy group (p:0.0004) in the long term (12 weeks). Therefore, prolotherapy is strongly recommended for long-term pain management. This study is relevant to a previous systematical review and meta-analysis study from Lin,2019 that prolotherapy is the best injection option to reduce pain in long-term follow-up (M. T. Lin et al., 2019).

In addition, prolotherapy is an injection technique based on regenerative methods that are becoming interested in treating musculoskeletal problems (Ersen et al., 2018). Prolotherapy contains dextrose (glucose) with varying concentrations that cause rupture osmosis in cells. Elevated glucose levels in the extracellular matrix irritate the tissue surrounding the injection site area. Therefore, it will cause an acute inflammatory response, stimulating fibroblast proliferation and following collagen formation. Finally, this mechanism resulting wound healing and tissue regeneration (Akpancar et al., 2019).

On the others hand, for the functional outcome, the three studies have a similarity in methods and periods of follow-up. The three studies have similarities in using the SPADI score and assessing the selected follow-up period of only 2-3 weeks. Unfortunately, our study did not show significant test results (p: 0.64). Several studies mentioned that physical rehabilitation could help relieve pain and return to regular functional activity, especially in shoulder stiffness due to rotator cuff abnormality (Akpancar et al., 2019). This study found that prolotherapy has the potential to decrease pain and increase functional outcomes in patients with rotator cuff tendinopathy.

Moreover, prolotherapy reduces pain in the long term (12 weeks) compared with physical rehabilitation. Ryösä et al. (2016) conducted a meta-analysis comparing conservative treatment or surgery in a patient with a rotator cuff tear. They mentioned that surgery is not more successful than conservative treatment in treating symptomatic rotator cuff tears. Therefore, a conservative approach is recommended as the initial treatment method, especially in rotator cuff tears (Ryösä et al., 2016).

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Many previous studies compared the type of injections. Hong JY was compared between corticosteroid and placebo(Hong et al., 2011), Chou compared sodium hyaluronate with normal saline (Chou et al., 2010), Kesikburun Platelet-rich plasma compared with placebo (Kesikburun et al., 2013), and many more. However, prolotherapy is a safe and effective treatment compared to standard therapies such as corticosteroid injections (tendon-ligament weakening or rupture, post-injection pain flare, soft tissue, or subcutaneous fat atrophy, and skin hypopigmentation). This condition is the opposite when using prolotherapy; dextrose can decrease laxity (C. L. Lin et al., 2019).

This study also has several limitations. There is heterogeneity in data sources. Several trials depended on diagnostic techniques alone in rotator cuff tendinopathy. Even physical tests may not indicate a complete or partial tear. Then, the difference in the injection dose between the studies can interfere with the quality of the study results.

Moreover, in several RCT studies, not mentioned specifically the outcome data, this condition may increase the probability of data extraction misperceptions. From the researcher's perspective, heterogeneous test results are due to the distribution of age, Ras/ethnicity, and differences in the number of participants in each study. Also, there is no standard physical rehabilitation used. Therefore, researchers assume this is the cause of the heterogeneity of the results in this study.

## CONCLUSION

Conclusion of this study, prolotherapy with physical rehabilitation can reduce pain in long-term (12 weeks) patients with PTRCT compared to physical rehabilitation only. A combination of prolotherapy and physical rehabilitation successfully reduce pain compared to physical rehabilitation only, while improving functional improvement did not significant.

## REFERENCES

Ainsworth, R., & Lewis, J. S. (2007). Exercise therapy for the conservative management of full thickness tears of the rotator cuff: a systematic review. *British Journal of Sports Medicine*, *41*(4), 200–210. https://doi.org/10.1136/BJSM.2006.032524

Akpancar, S., Örsçelik, A., Seven, M. M., & Koca, K. (2019). The effectiveness of prolotherapy on failed rotator cuff repair surgery. *Turkish Journal of Physical Medicine and Rehabilitation*, *65*(4), 394–401. https://doi.org/10.5606/TFTRD.2020.3222

Bang, M. D., & Deyle, G. D. (2000). Comparison of supervised exercise with and without manual physical therapy for patients with shoulder impingement syndrome. *The Journal of Orthopaedic and Sports Physical Therapy*, *30*(3), 126–137. https://doi.org/10.2519/JOSPT.2000.30.3.126

Bertrand, H., Reeves, K. D., Bennett, C. J., Bicknell, S., & Cheng, A. L. (2016). Dextrose prolotherapy versus control injections in painful rotator cuff tendinopathy. *Archives of Physical Medicine and Rehabilitation*, *97*(1), 17–25. https://doi.org/10.1016/j.apmr.2015.08.412

Catapano, M., Zhang, K., Mittal, N., Sangha, H., Onishi, K., & de SA, D. (2020). Effectiveness of Dextrose Prolotherapy for Rotator Cuff Tendinopathy: A Systematic Review. *PM&R*, *12*(3), 288–300. https://doi.org/10.1002/PMRJ.12268

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

Chou, W. Y., Ko, J. Y., Wang, F. S., Huang, C. C., Wong, T., Wang, C. J., & Chang, H. E. (2010). Effect of sodium hyaluronate treatment on rotator cuff lesions without complete tears: A randomized, double-blind, placebo-controlled study. *Journal of Shoulder and Elbow Surgery*, *19*(4), 557–563. https://doi.org/10.1016/j.jse.2009.08.006

de Sanctis, E. G., Franceschetti, E., de Dona, F., Palumbo, A., Paciotti, M., & Franceschi, F. (2020). The Efficacy of Injections for Partial Rotator Cuff Tears: A Systematic Review. *Journal of Clinical Medicine 2021, Vol. 10, Page 51*, *10*(1), 51. https://doi.org/10.3390/JCM10010051

Desjardins-Charbonneau, A., Roy, J. S., Dionne, C. E., Frémont, P., Macdermid, J. C., & Desmeules, F. (2015). The efficacy of manual therapy for rotator cuff tendinopathy: A systematic review and meta-analysis. *Journal of Orthopaedic and Sports Physical Therapy*, *45*(5), 330–350. https://doi.org/10.2519/JOSPT.2015.5455/ASSET/IMAGES/LARGE/JOSPT-330-FIG008.JPEG

George, J., Li, S. C. N., Jaafar, Z., & Hamid, M. S. A. (2018). Comparative Effectiveness of Ultrasound-Guided Intratendinous Prolotherapy Injection with Conventional Treatment to Treat Focal Supraspinatus Tendinosis. *Scientifica*, *2018*. https://doi.org/10.1155/2018/4384159

Hauser, R. A., Lackner, J. B., Steilen-Matias, D., & Harris, D. K. (2016). A systematic review of dextrose prolotherapy for chronic musculoskeletal pain. *Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders*, *9*, 139–159. https://doi.org/10.4137/CMAMD.S39160/ASSET/IMAGES/LARGE/10.4137_CMAMD.S39160-FIG2.JPEG

Hong, J. Y., Yoon, S. H., Moon, D. J., Kwack, K. S., Joen, B., & Lee, H. Y. (2011). Comparison of high- and low-dose corticosteroid in subacromial injection for periarticular shoulder disorder: A randomized, triple-blind, placebo-controlled trial. *Archives of Physical Medicine and Rehabilitation*, *92*(12), 1951–1960. https://doi.org/10.1016/j.apmr.2011.06.033

Hutton, B., Salanti, G., Caldwell, D. M., Chaimani, A., Schmid, C. H., Cameron, C., Ioannidis, J. P. A., Straus, S., Thorlund, K., Jansen, J. P., Mulrow, C., Catala-Lopez, F., Gotzsche, P. C., Dickersin, K., Boutron, I., Altman, D. G., & Moher, D. (2015). The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. *Https://Doi.Org/10.7326/M14-2385*, *162*(11), 777–784. https://doi.org/10.7326/M14-2385

Kazempour Mofrad, M., Rezasoltani, Z., Dadarkhah, A., Kazempour Mofrad, R., Abdorrazaghi, F., & Azizi, S. (2021). Periarticular Neurofascial Dextrose Prolotherapy Versus Physiotherapy for the Treatment of Chronic Rotator Cuff Tendinopathy: Randomized Clinical Trial. *Journal of Clinical Rheumatology*, *27*(4), 136–142. https://doi.org/10.1097/RHU.0000000000001218

Kesikburun, S., Tan, A. K., Yilmaz, B., Yaşar, E., & Yazicioğlu, K. (2013). Platelet-rich plasma injections in the treatment of chronic rotator cuff tendinopathy: A randomized controlled trial with 1-year follow-up. *American Journal of Sports Medicine*, *41*(11), 2609–2615. https://doi.org/10.1177/0363546513496542/

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

A S S E T / I M A G E S / LARGE/10.1177_0363546513496542-FIG2.JPEG

Kim, Y. S., Park, J. Y., Lee, C. S., & Lee, S. J. (2012). Does hyaluronate injection work in shoulder disease in early stage? A multicenter, randomized, single blind and open comparative clinical study. *Journal of Shoulder and Elbow Surgery*, *21*(6), 722–727. https://doi.org/10.1016/j.jse.2011.11.009

Kuhn, J. E. (2009). Exercise in the treatment of rotator cuff impingement: A systematic review and a synthesized evidence-based rehabilitation protocol. *Journal of Shoulder and Elbow Surgery*, *18*(1), 138–160. https://doi.org/10.1016/j.jse.2008.06.004

Lin, C. L., Huang, C. C., & Huang, S. W. (2019). Effects of hypertonic dextrose injection in chronic supraspinatus tendinopathy of the shoulder: A randomized placebo-controlled trial. *European Journal of Physical and Rehabilitation Medicine*, *55*(4), 480–487. https://doi.org/10.23736/S1973-9087.18.05379-0

Lin, K. M., Wang, D., & Dines, J. S. (2018). Injection Therapies for Rotator Cuff Disease. *Orthopedic Clinics of North America*, *49*(2), 231–239. https://doi.org/10.1016/J.OCL.2017.11.010

Lin, M. T., Chiang, C. F., Wu, C. H., Huang, Y. T., Tu, Y. K., & Wang, T. G. (2019). Comparative Effectiveness of Injection Therapies in Rotator Cuff Tendinopathy: A Systematic Review, Pairwise and Network Meta-analysis of Randomized Controlled Trials. *Archives of Physical Medicine and Rehabilitation*, *100*(2), 336-349.e15. https://doi.org/10.1016/j.apmr.2018.06.028

Matthewson, G., Beach, C. J., Nelson, A. A., Woodmass, J. M., Ono, Y., Boorman, R. S., Lo, I. K. Y., & Thornton, G. M. (2015). Partial Thickness Rotator Cuff Tears: Current Concepts. *Advances in Orthopedics*, *2015*. https://doi.org/10.1155/2015/458786

Min, K. S., st. Pierre, P., Ryan, P. M., Marchant, B. G., Wilson, C. J., & Arrington, E. D. (2013). A double-blind randomized controlled trial comparing the effects of subacromial injection with corticosteroid versus NSAID in patients with shoulder impingement syndrome. *Journal of Shoulder and Elbow Surgery*, *22*(5), 595–601. https://doi.org/10.1016/j.jse.2012.08.026

Original Article Turk ; Ersen, Ö., Koca, K., Akpancar, S., Seven, M. M., Akyıldız, F., & Yıldız, Y. (2018). A randomized-controlled trial of prolotherapy injections in the treatment of plantar fasciitis. *Turk J Phys Med Rehab*, *64*(1), 59–65. https://doi.org/10.5606/tftrd.2018.944

Park, H.-S., Choi, K.-H., Lee, H.-J., & Kim, Y.-S. (2020). Rotator cuff tear with joint stiffness: a review of current treatment and rehabilitation. *Clinics in Shoulder and Elbow*, *23*(2), 109–116. https://doi.org/10.5397/CISE.2020.00143

Penning, L. I. F., de Bie, R. A., & Walenkamp, G. H. I. M. (2012). The effectiveness of injections of hyaluronic acid or corticosteroid in patients with subacromial impingement: A three-arm randomised controlled trial. *Journal of Bone and Joint Surgery - Series B*, *94 B*(9), 1246–1252. https://doi.org/10.1302/0301-620X.94B9.28750/ASSET/IMAGES/LARGE/28750-GALLEYFIG2.JPEG

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

Rashid, M. S., Cooper, C., Cook, J., Cooper, D., Dakin, S. G., Snelling, S., & Carr, A. J. (2017). Increasing age and tear size reduce rotator cuff repair healing rate at 1 year. *New Pub: Medical Journals Sweden*, *88*(6), 606–611. https://doi.org/10.1080/17453674.2017.1370844

Ryösä, A., Laimi, K., Äärimaa, V., Lehtimäki, K., Kukkonen, J., & Saltychev, M. (2016). Surgery or conservative treatment for rotator cuff tear: a meta-analysis. *Https://Doi.Org/10.1080/09638288.2016.1198431*, *39*(14), 1357–1363. https://doi.org/10.1080/09638288.2016.1198431

Sambandam, S. N., Khanna, V., Gul, A., & Mounasamy, V. (2015). Rotator cuff tears: An evidence based approach. *Http://Www.Wjgnet.Com/*, *6*(11), 902–918. https://doi.org/10.5312/WJO.V6.I11.902

Sari, A., & Eroglu, A. (2020). Comparison of ultrasound-guided platelet-rich plasma, prolotherapy, and corticosteroid injections in rotator cuff lesions. *Journal of Back and Musculoskeletal Rehabilitation*, *33*(3), 387–396. https://doi.org/10.3233/BMR-191519

Schmidt, C. C., Jarrett, C. D., & Brown, B. T. (2015). Management of rotator cuff tears. *Journal of Hand Surgery*, *40*(2), 399–408. https://doi.org/10.1016/j.jhsa.2014.06.122

Seven, M. M., Ersen, O., Akpancar, S., Ozkan, H., Turkkan, S., Yıldız, Y., & Koca, K. (2017). Effectiveness of prolotherapy in the treatment of chronic rotator cuff lesions. *Orthopaedics & Traumatology: Surgery & Research*, *103*(3), 427–433. https://doi.org/10.1016/J.OTSR.2017.01.003

Smith, K. L., Harryman, D. T., Antoniou, J., Campbell, B., Sidles, J. A., & Matsen, F. A. (2000). A prospective, multipractice study of shoulder function and health status in patients with documented rotator cuff tears. *Journal of Shoulder and Elbow Surgery*, *9*(5), 395–402. https://doi.org/10.1067/MSE.2000.108962