

# BMJ Open Effectiveness of subacromial injections in rotator cuff lesions: systematic review and meta-analysis protocol

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## ABSTRACT

**Introduction** Subacromial injections are therapeutic options for rotator cuff injuries, with consistent results not well established yet for each drug applied. The objective of this systematic review and meta-analysis is to analyse the effectiveness of the substances used in subacromial injections for the treatment of rotator cuff injuries and shoulder impingement syndrome, considering the functional gain and pain improvement of the shoulder.

**Methods and analysis** Beginning in November 2022, we will perform a detailed search using the MEDLINE/PubMed, EMBASE, Cochrane Central Register of Controlled Trials and LILACS databases. Relevant grey literature (reference lists, conference abstracts and academic papers) will also be included.

Two reviewers will independently screen and extract the information from the literature. Bias and quality of the included studies will be evaluated using the risk of bias assessment tool provided by the Cochrane Collaboration. Statistical analyses will be performed using Review Manager V.5.4 software.

**Ethics and dissemination** Approval and patient informed consent are not required because we will only include published literature. The results of this research will be disseminated in a peer-reviewed journal and likely through other scientific events.

**PROSPERO registration number** CRD42020199292.

## INTRODUCTION

Rotator cuff injuries (RCIs) can range from inflammatory processes to partial-thickness and full-thickness tears.<sup>1</sup> They are the most frequent cause of shoulder pain and the third most frequent complaint in orthopaedic care.<sup>2</sup> There are several treatment options for RCI, which can be subdivided into non-surgical and surgical methods. As for non-surgical management, oral medications and physiotherapy are the most commonly used, although acupuncture, laser, ultrasound and extracorporeal shock wave therapy are also used as adjuvants.<sup>3</sup> In addition, there are interventional therapy options such as subacromial injections and peripheral nerve blocks.<sup>4</sup> Many possibilities of subacromial injections have been

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The strength of this systematic review lies in the fact that there will be no restriction in the selection of studies based on the language and/or publication date.
- ⇒ The studies will include randomised and quasi-randomised clinical trials and will be evaluated using large databases, resulting in a better level of evidence.
- ⇒ Pairwise and network meta-analyses will be performed, if possible, to ensure more applicable results.
- ⇒ This systematic review protocol is limited to partial tears and rotator cuff tendinopathies. Therefore, future conclusions cannot be extended to complete lesions.

described for the treatment of shoulder injuries, including injection therapies with corticosteroids, prolotherapy, platelet-rich plasma (PRP) and hyaluronic acid.<sup>5</sup> Corticosteroid injections are used to relieve pain and/or inflammation in a wide variety of musculoskeletal disorders,<sup>6–9</sup> but the mechanism underlying their positive effect on tendinopathy remains unclear.<sup>10</sup> Prolotherapy consists of solutions with a concentration of greater than 10% glucose and, through an osmotic gradient, leads to an influx of growth factors and inflammatory cells where it is injected, which can support tissue healing cascade.<sup>11</sup> Another subacromial injection possibility is PRP, which is an autologous concentration of platelets and associated growth factors produced by the centrifugal separation of whole blood.<sup>12–14</sup> These factors have been shown to promote cell recruitment, proliferation and angiogenesis.<sup>15</sup> PRP may induce a transient inflammatory event that leads to a regenerative response.<sup>16</sup> In addition to these substances, hyaluronic acid is also used in subacromial injections. Hyaluronic acid not only protects and covers the articular cartilage but also plays a role in the suppression of inflammatory processes, pain relief, inhibition of adhesion and tissue recovery.<sup>17 18</sup>

However, the current evidence for these therapies remains controversial both in

**Table 1** Search strategies presented to the main databases

Databases	Search strategy
MEDLINE/PubMed	(shoulder Impingement syndrome OR subacromial bursitis OR subacromial impingement OR rotator cuff injuries OR Rotator Cuff tendinosis OR rotator cuff OR shoulder pain OR supraspinatus OR infraspinatus OR subscapular OR teres) AND (hyaluronic acid OR acid, hyaluronic OR amo vitrax OR vitrax, amo OR biolon OR etamucine OR hyaluronan OR hyvisc OR luronit OR sodium hyaluronate OR hyaluronate, sodium OR hyaluronate sodium OR amvisc OR healon platelet-rich plasma OR plasma, platelet-rich OR platelet rich plasma OR PRP OR corticoid OR corticosteroid injection OR prolotherapy OR dextrose injection) Filters: humans, randomized controlled trial, controlled clinical trial, randomized
The Cochrane Library	#1 (shoulder Impingement syndrome):ti,ab,kw #2 (subacromial bursitis): ti,ab,kw #3 (Rotator Cuff Tendinosis): ti,ab,kw #4 (subacromial impingement): ti,ab,kw #5 (rotator cuff injuries): ti,ab,kw #6 (hyaluronate sodium):ti,ab,kw #7 (platelet-rich plasma):ti,ab,kw #8 (corticoid):ti,ab,kw #9 (prolotherapy) #10 (#1 OR #2 OR #3 OR #4 OR #5) #11 (#6 OR #7 OR #8 OR #9) #12 (#10 AND #11)
EMBASE	("shoulder Impingement syndrome" OR "subacromial bursitis" OR "subacromial impingement" OR "rotator cuff injuries" OR "Rotator Cuff Tendinosis" OR "rotator cuff" OR "shoulder pain" OR "supraspinatus" OR "infraspinatus" OR "subscapular" OR "teres") AND ("OR acid, hyaluronic" OR "amo vitrax" OR "vitrax, amo" OR "biolon" OR "etamucine" OR "hyaluronan" OR "hyvisc" OR "luronit" OR "sodium hyaluronate" OR "hyaluronate, sodium" OR "hyaluronate sodium" OR "amvisc" OR "healon platelet-rich plasma" OR "plasma, platelet-rich" OR "platelet rich plasma" OR "PRP" OR "corticoid" OR "corticosteroid injection" OR "prolotherapy" OR "dextrose injection")
LILACS	tw=shoulder Impingement syndrome [Palavras] or "rotator cuff injuries" [Palavras] AND tw=hyaluronate sodium[Palavras] or platelet-rich plasma[Palavras] or corticoid[Palavras] or prolotherapy[Palavras]

terms of effectiveness and dosage; no clear consensus can be found regarding the frequency of injections for partial rotator cuff tears or the most effective therapy for these lesions in the short, medium and long term.<sup>19</sup> The latest systematic review and meta-analysis on the subject was published in 2019, with a deadline for data collection in September 2017, quasi-randomised clinical trials were excluded and the LILACS search platform was not included.<sup>20</sup> Since then, several randomised clinical trials have been published, and there is a need for a subject update to guide clinical practice concerning intervention that is the most effective treatment for RCIs.

## Objectives

This study aims to analyse the effectiveness of subacromial infiltration of drugs and biologicals (corticosteroids, prolotherapy, hyaluronic acid and PRP) for rotator cuff lesions, considering improvements in shoulder pain and function.

## METHODS

### Study guidelines and registration

The systematic review and meta-analysis will be performed following the Cochrane Handbook for Systematic Reviews of Interventions and will be reported in compliance with

the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>21 22</sup> The systematic review will begin on 10 November 2022 and the expected date to finish is September 2023. A predetermined written protocol is registered on the PROSPERO platform under number CRD42020199292.

### Patient and public involvement

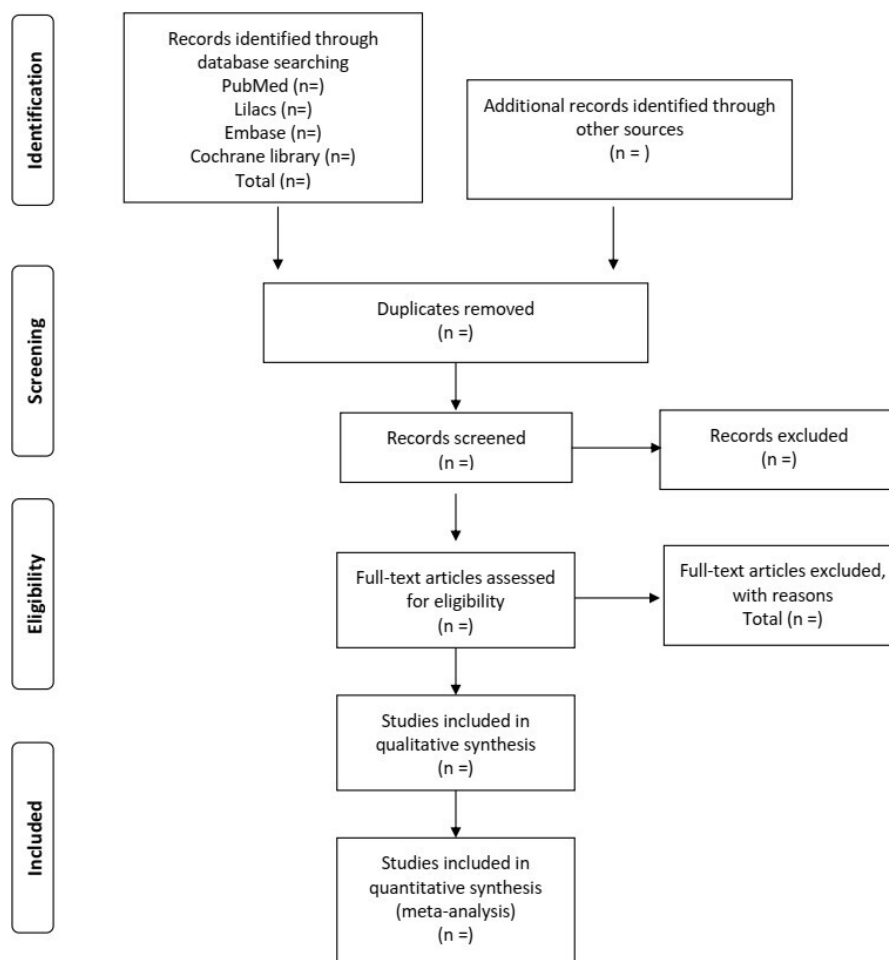
This protocol is for a systematic review and meta-analysis and, therefore, will analyse randomised clinical trials. As there is no involvement of patients, there is no requirement for informed consent.

### Eligibility criteria

Randomised or quasi-randomised clinical trials, studies performed in humans, and studies addressing subacromial injection modalities of drugs and biologicals (corticosteroids, hyaluronic acid, prolotherapy or PRP) will be included. There will be no restrictions on the year or the language of publication.

### Population

We will include studies involving adults over 18 years of age with RCI, without a history of shoulder surgery or other shoulder injuries. Full-thickness rotator cuff tears,



**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart.

confirmed by imaging methods (ultrasound or nuclear MRI), will be excluded.

### Intervention

The analysed interventions will be the subacromial injection of drugs or biologicals (corticosteroids, hyaluronic acid, PRP and prolotherapy).

### Comparator

The intended comparisons, through pairwise meta-analysis, are injections (corticosteroids, hyaluronic acid, PRP and prolotherapy) versus placebo (0.9% saline) or control; and hyaluronic acid versus PRP versus corticosteroid versus prolotherapy with network meta-analysis.

### Outcomes

The primary outcome will be the assessment of improvement in shoulder pain after a subacromial injection measured by the pain visual analogue scale (VAS), and improvement in function using standardised scores (Constant-Murley Score (CMS), Disabilities of the Arm, Shoulder and Hand (DASH), Oxford Shoulder Score (OSS), American Shoulder and Elbow Surgeons Shoulder Score (ASES), and Shoulder Pain, Disability Index (SPADI) and University of California at Los Angeles Shoulder Score (UCLA)). We will evaluate these

results in the short, medium, and long term which will be defined as up to 3 months, 3–12 months, and more than 12 months, respectively.

The secondary outcome will be the evaluation of the safety of the substances used in the analysis of complications after subacromial injection. We will separate possible adverse effects into minor complications, including those that do not require hospitalisation, and major complications in which the patient needs to be admitted to the hospital.

In addition to the primary and secondary objectives of the study, we will also assess radiological outcomes after the injections. In studies that use MRI in patient follow-up, we will assess whether there was healing or progression of the RCI, through tendon thickness, or whether there was improvement in tendinopathy due to the reduction of hypersignal or intratendinous heterogeneity. Furthermore, if data are available, we will conduct a subgroup analysis of interventions performed with and without the use of ultrasound.

### Study types

This systematic review and meta-analysis will only include randomised controlled trials (RCTs) and quasi-RCTs. Other studies will be excluded.

## Search strategy

We will search the electronic databases until March 2022 for published literature of RCTs to identify eligible studies. These include PubMed, Cochrane Library, LILACS and EMBASE databases. We will also search reference lists, conference proceedings and abstracts, academic papers, including theses and dissertations. The search strategy is presented in [table 1](#).

## Study selection

The screening steps for the articles will be performed by two authors independently, and duplicate studies will be identified and excluded. An analysis of titles and abstracts and full reading will be performed by two researchers, according to the defined eligibility criteria. Any disagreements will be solved by members of the research team. When selecting potentially relevant studies, the articles will be read in full by both researchers and those that do not fit the research protocol will be excluded. Reviewers will keep an Excel spreadsheet to record the decision-making, containing an explanation regarding the inclusion or exclusion of the study. If any study is incomplete regarding the necessary information, the researchers will send an email to the author for clarification, and if the original author does not respond, we will designate the study as 'missing information'.

The details of the entire selection procedure are shown in the PRISMA flow chart in [figure 1](#).

## Data extraction

Data extraction will be conducted using Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA). Two researchers will extract the following data: title, author, year of publication and place, study design and intervention follow-up time, sample size, details of the diagnosis for RCI and subacromial impingement syndrome, characteristics of the intervention (corticosteroid, PRP, prolotherapy or hyaluronic acid), number of injections and if it was ultrasound guided, and outcome or outcome measures. In addition, the location of the infiltration (whether subacromial or intratendinous) will be pointed out. Patients will be stratified in terms of partial rotator cuff tears and impingement syndrome, the former being characterised by a partial discontinuity of the tendon and the latter being defined by inflammation.

## Risk of bias assessment

The risk of bias in the included studies will be assessed by two researchers using the Risk of Bias 2 tool, a revised Cochrane risk-of-bias tool for randomised trials.<sup>23</sup> The following five methodological domains will be evaluated for risk of bias: (1) arising from the randomisation process, (2) due to deviations from the intended interventions, (3) due to missing outcome data, (4) in measurement of the outcome and (5) in selection of the reported result. A 'low' risk of bias judgement will be assigned to each domain, 'high' risk of bias or 'some concerns'; the latter reflecting a lack of information or uncertainty about the

potential for bias. Disagreements between the authors regarding the risk of bias for each domain will be resolved by consensus. The quality of evidence for each outcome will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation.<sup>24 25</sup> The quality of the studies' outcomes will be classified into four categories: high, moderate, low or very low.

## Statistical analyses

Population size, mean and SD values of pain reduction and functional improvement will be used to calculate the meta-analysis. The results will be expressed as weighted mean differences with 95% CIs. A random-effects meta-analysis will be performed. Heterogeneity will be defined based on  $I^2$  values as follows: 25%, low heterogeneity; 50%, moderate heterogeneity; and 90%, high heterogeneity. All statistical analyses will be performed using Review Manager V.5.4 software, with p value of <0.05 considered statistically significant.

## DISCUSSION

RCIs are the most frequent cause of shoulder pain, and there are several possibilities for treatment. The evaluation of the effectiveness of these treatments in clinical evidence is essential to determine the best treatment for patients. Since joint and periarticular injection is a minimally invasive, fast and safe method, it has been widely explored in orthopaedics, with variable results for each joint and substance used. We will select the main drugs and biologicals used in clinical practice to evaluate their effectiveness in terms of pain relief and functional improvement. We chose to use the VAS because it is the most used for pain assessment in randomised clinical trials and easy to understand. For functional improvement, we will use the most validated scores for assessing shoulder function: the CMS, DASH, ASES, OSS, UCLA and SPADI. Regarding the evaluation period, we chose to separate into short-term, medium-term and long-term periods, corresponding to up to 3 months, 3–12 months and longer than 12 months, respectively. We believe that this method will provide better evidence regarding the consistency of drugs and biologicals used in subacromial injections.

Considering the various treatment techniques for RCIs, we believe that we must guide our clinical practice according to what is most current and with the highest level of scientific evidence. Therefore, a systematic review of subacromial infiltrations for these shoulder diseases is convenient and will be a guide to many experts.

## ETHICS AND DISSEMINATION

Although this study did not involve humans, it was submitted to and approved by the Research Ethics Committee of the Federal University of São Paulo under approval number 8715280520. We believe that we will obtain relevant results based on scientific evidence



for the management of partial rotator cuff tears using subacromial injections. Therefore, the conclusions of this systematic review may benefit both physicians and patients, thereby supporting the use of efficient therapies. The results of this research will be disseminated in a peer-reviewed journal and likely through other scientific events.

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**Contributors** LTG—submitting author and corresponding author. FTM, JCB, FF, TSP and MJST—authorship. LTG and MJST devised the project and collected data in the literature about the content covered. MJST conceived the study and was in charge of overall direction. FTM structured the manuscript according to scientific norms. LTG and TSP contributed to the design and wrote the manuscript. They will evaluate the data and formulate the planned meta-analyses. JCB and FF reviewed the study proposal and contributed to implementation of the research.

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**Competing interests** None declared.

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**Patient consent for publication** Not required.

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