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DOKTORI ISKOLA

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# WENINGER VIKTOR

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Programvezető: Dr. Szőke György, egyetemi tanár

Témavezető: Dr. Skaliczki Gábor, egyetemi adjunktus

# EVIDENCE-BASED STRATEGIES FOR OPTIMIZING SHOULDER TREATMENT OUTCOMES: FROM INJECTIONS TO ANTIMICROBIALS

**Ph.D. Thesis**


## Viktor Weninger, M.D.

Translational Medicine Program

Surgical Medicine Division

SEMMELWEIS UNIVERSITY


| | |
|---|---|
| Supervisor: | Gábor Skaliczki M.D., Ph.D. |
| Official reviewers: | Imre Antal M.D., Ph.D |
| | Ling Qin M.D., Ph.D. Dsc. |
| Head of the Complex Examination Committee: | Gábor Varga Ph.D. |
| | László Bucsi M.D., Ph.D. |
| Members of the Complex Examination Committee: | Miklós Szendrői M.D., Ph.D. Dsc. |
| | Daniel Kendoff M.D., Ph.D. |
| | Nelli Farkas M.D: Ph.D. |

Budapest

2025

***"There are no mistakes, only opportunities."***

*Tina Frey*

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## 1. LIST OF ABBREVIATIONS

*ADRC – adipose-derived regenerative cells*

*ASES – American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form*

*BPO – Benzoyl peroxide*

*CHG – Chlorhexidine*

*CI – Confidence Interval*

*CLI – Clindmycin*

*CMS – Constant Murley Score*

*C. acnes – Cutibacterium acnes*

*HA – Hyaluronic acid*

*MD – Mean Difference*

*MN – Miconazole Nitrate*

*MRI – Magnetic Resonance Imaging*

*PRP – Platelet-rich plasma*

*PRISMA*-Preferred Reporting Items for Systematic Reviews and Meta-Analyses

*PTRCT – Partial-Thickness Rotator Cuff Tears*

*SD – Standard Deviation*

*SE – Standard Error*

*VAS – Visual Analog Scale*

## *2.* STUDENT PROFILE

### 2.1.Vision Statement.

To promote safer, evidence-based shoulder care by reducing reliance on corticosteroids and implementing targeted skin antisepsis to minimize *Cutibacterium acnes* (C. acnes) colonization, resulting in fewer patient side effects, lower infection rates, and improved overall clinical outcomes

### 2.2.Mission statement

Throughout my Ph.D. studies, I have been driven by a commitment to re-examine established knowledge and to explore alternative possibilities—challenging 'what we know to be true' and pursuing 'what could have been.' My goal is not only to advance scientific understanding but to ensure that these insights are accessible, applicable, and beneficial to a broader community, beyond the confines of academia.

### 2.3.Specific goals

During my doctoral studies, my specific goals are to determine the optimal treatment for partial rotator cuff tears via injection and to identify the most effective adjunctive therapy for *C. acnes* infections during shoulder surgery.

### 2.4.Scientometrics

| | |
|---|---|
| **Number of all publications:** | **4** |
| **Cumulative IF:** | 18.20 |
| **Av IF/publication:** | 4.55 |
| **Ranking Scimago:** | D1: 3, Q1: 1 |
| **Number of publications related to the subject of the thesis:** | 2 |
| **Cumulative IF:** | 9.2 |
| **Av IF/publication:** | 4.6 |
| **Ranking Scimago:** | D1: 2 |
| **Number of citations on Google Scholar:** | 5 |
| **Number of citations on MTMT (independent):** | 3 |
| **H-index:** | 1 |

### 2.5.Future Plans

To promote safer, evidence-based shoulder care by reducing reliance on corticosteroids and implementing targeted skin antisepsis to minimize *C. acnes* colonization, resulting in fewer patient side effects, lower infection rates, and improved overall clinical outcomes. Throughout my Ph.D. studies, I have been driven by a commitment to re-examine established knowledge and to explore alternative possibilities—challenging 'what we know to be true' and pursuing 'what could have been.' My goal is not only to advance scientific understanding but to ensure that these insights are accessible, applicable, and beneficial to a broader community, beyond the confines of academia.

During my doctoral studies, my specific goals are to determine the optimal treatment for partial rotator cuff tears via injection and to identify the most effective adjunctive treatment for *C. acnes* infections during shoulder surgery.

## 3. SUMMARY OF THE PHD

The management of shoulder disorders requires both conservative and perioperative strategies to improve patient outcomes. This thesis presents two complementary network meta-analyses addressing key aspects of shoulder care: injection therapies for partial rotator cuff tears and preoperative skin preparation to prevent *Cutibacterium acnes*infections in surgery.

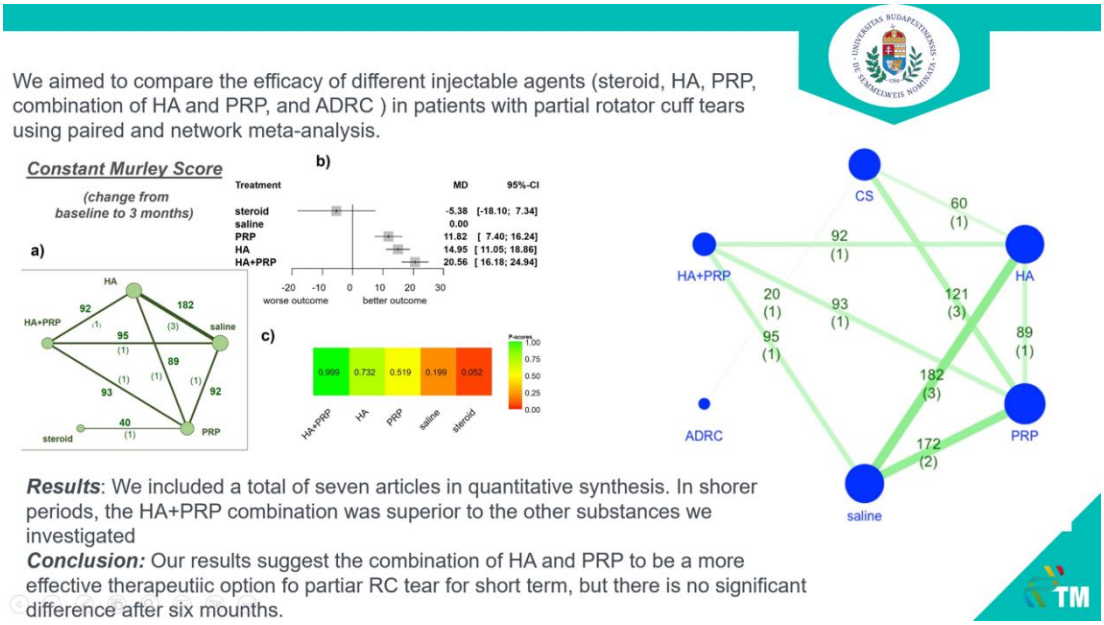
The first analysis compared corticosteroids, platelet-rich plasma (PRP), hyaluronic acid (HA), their combination, and adipose-derived regenerative cells. Results showed that PRP combined with HA achieved the most consistent improvements in pain relief and function, especially in the short term, while corticosteroids raised concerns about tendon damage and systemic effects. Interestingly, saline injections outperformed steroids in the very early phase, though not at longer follow-up. These findings highlight the potential of regenerative biologic therapies in musculoskeletal care.

The second analysis examined methods to reduce *C. acnes* colonization, a frequent source of postoperative shoulder infections. Among seven preoperative skin preparation strategies, 5% benzoyl peroxide (BPO), alone or with clindamycin, was most effective, outperforming standard alcohol- or chlorhexidine-based antiseptics.

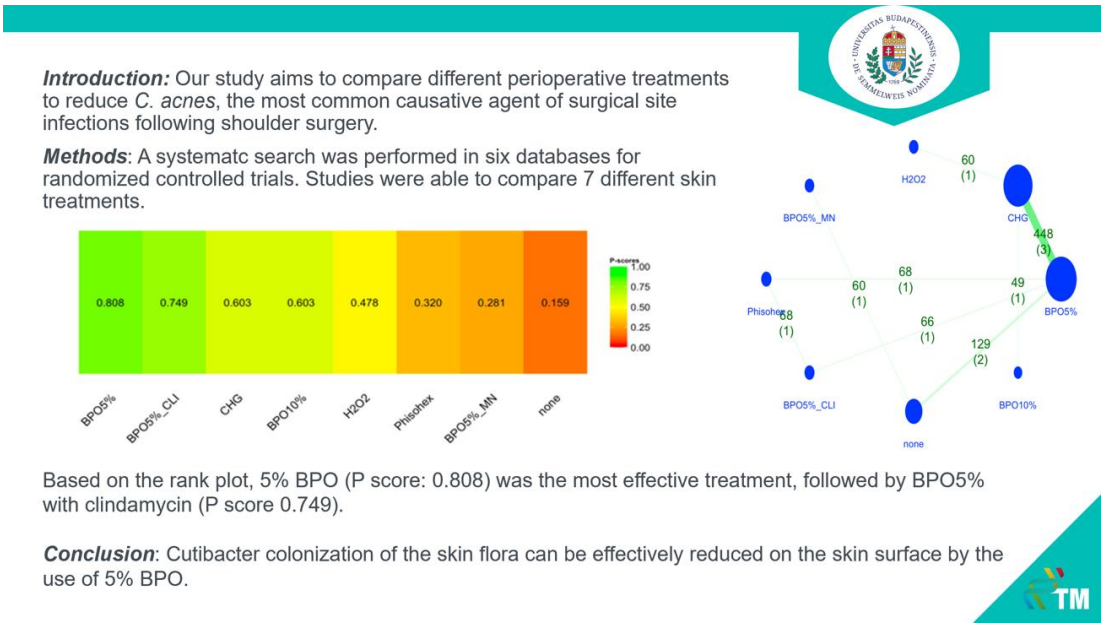
Together, these studies suggest a shift toward biologically informed strategies: regenerative injection therapies such as PRP+HA for conservative management and benzoyl peroxide protocols for infection prevention. This integrated approach aligns efficacy with safety and represents a pathway to more personalized and evidence-based orthopedic care.

## 4. GRAPHICAL ABSTRACT

Viktor Weninger et al., Hyaluronate acid plus platelet-rich plasma is superior to steroids for pain relief less than 6 months using injection therapy of partial rotator cuff tears: A systematic review and network meta-analysis, *Arthroscopy: The Journal of Arthroscopic & Related Surgery, 2025*




Viktor Weninger et al., 5% benzoyl peroxide is the most efficient in reducing the cutibacterium flora of the shoulder skin: a network meta-analysis, *EFORT Open Reviews, 2025*



## 5. INTRODUCTION

### 5.1.What is the topic

This research focuses on two interrelated aspects of shoulder care:

- The non-surgical treatment of partial-thickness rotator cuff tears (PTRCTs) through various injectable agents, including corticosteroids, platelet-rich plasma (PRP), hyaluronic acid (HA), and adipose-derived regenerative cells (ADRC) [1, 2].
- The prevention of postoperative infections in shoulder surgery, particularly those caused by *Cutibacterium acnes* (*C. acnes*) [3, 4], by comparing the effectiveness of different preoperative skin antiseptic preparations [5-7]. Both areas are critical in orthopedic practice and have major implications for patient safety, functional recovery, and long-term treatment success [7].

### 5.2.What is the problem to solve?

Despite their widespread use, the most effective injectable therapy for PTRCTs remains unclear [8]. Corticosteroids, although widely accepted as the standard of care, carry significant long-term risks, including tendon degeneration and increased revision rates [9-12]. Emerging biologic therapies such as PRP and HA offer potential benefits, but a comprehensive comparison is lacking in the literature. Similarly, while surgical site infections (SSIs) caused by *C. acnes* represent a major complication in shoulder surgery, conventional antiseptic protocols such as chlorhexidine or alcohol-based preparations have limited efficacy against this bacterium. *C. acnes* resides deep within sebaceous glands and can adhere to implants, often going undetected during surgery [4, 13]. There is no consensus on the optimal skin preparation to prevent these infections [3, 4, 14, 15].

### 5.3.What is the importance of the topic?

PTRCTs are highly prevalent, especially among the elderly population, and significantly impact quality of life through pain and loss of function. Identifying the most effective, least harmful injection therapy could lead to more targeted, regenerative, and sustainable treatment strategies [16, 17]. At the same time, postoperative infections—particularly those related to C. acnes—can severely compromise surgical outcomes, leading to implant failure, prolonged recovery, and additional procedures [3]. Improving infection prevention protocols through more effective antiseptic strategies is essential for patient

safety, especially given the increasing volume of shoulder surgeries globally [7]. Together, these topics address both the therapeutic and preventive dimensions of modern shoulder care.

### 5.4.What would be the impact of our research results?

This research may help establish clearer clinical guidelines for the use of biologic injection therapies in the management of PTRCTs. By identifying the most effective agent or combination (e.g., PRP + HA), the study can contribute to more individualized and safer treatment decisions, potentially reducing reliance on corticosteroids and improving long-term outcomes [18]. In parallel, identifying the most effective antiseptic—such as 5% benzoyl peroxide—against *C. acnes* may provide new standards for preoperative skin preparation in shoulder surgery. This could reduce infection rates, lower revision surgery risks, and ultimately improve surgical safety and cost-effectiveness [4].

### 5.5.Further Introductory

A brief anatomical overview would help contextualize the vulnerability of the rotator cuff to age-related degeneration and mechanical overload, providing the basis for understanding tear development[19, 20]. This section could detail the intrinsic and extrinsic factors that contribute to partial tears, including biological degeneration and biomechanical stress [21].

An overview of the microbiological characteristics of *C. acnes*, its role in prosthetic infections, biofilm formation, and resistance to conventional antiseptics would support the rationale for alternative skin preparation methods [22]. Reviewing existing clinical guidelines, practices, and controversies around injection therapies and antiseptic protocols would clearly define the unmet clinical needs that this research addresses.

## 6. OBJECTIVES

### 6.1.Study I.

This study aims to compare the clinical effectiveness of various injectable therapies—including corticosteroids, platelet-rich plasma (PRP), hyaluronic acid (HA), their combination, and adipose-derived regenerative cells (ADRC)—in the conservative treatment of partial-thickness rotator cuff tears (PTRCTs) [23-29]. Through a paired and network meta-analysis, we aim to identify which injectable agent provides the greatest benefit in terms of pain relief and functional improvement, while minimizing adverse effects. The ultimate goal is to determine whether biologic alternatives can offer a safer and more effective treatment option than corticosteroids, which are currently considered the standard of care [30].

### 6.2.Study II.

The objective of this study is to evaluate and compare the effectiveness of currently available preoperative skin antiseptic agents in reducing Cutibacterium acnes colonization on the shoulder. Given the high prevalence of *C. acnes*-related postoperative infections and the limited efficacy of conventional antiseptic agents, this study aims to evaluate whether the addition of peroxide-based compounds to alcohol-based antiseptics enhances decolonization compared with alcohol- or chlorhexidine-based preparations [5, 13, 31-42]. Our goal is to provide evidence that may provide improved infection prevention protocols in shoulder surgery [43].

## 7. METHODS

Both studies were conducted with full adherence to the Cochrane Handbook for Systematic Reviews of Interventions , and were protocolized according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement [44]. Both studies were also prospectively registered on the International Prospective Register of Systematic Reviews (PROSPERO), with the following identifiers for the first and second study, respectively: CRD42021285416, CRD42022290391.

### 7.1.Study I

#### 7.1.1. Search Strategy

Contrary as stated in the protocol we did not find studies comparing collagen and nonsteroidal anti-inflammatory drugs, while we included ADRC treatment. We did not have enough data to investigate the Western Ontario Rotator Cuff Index, range of motion, side effects, infections and complications. A systematic search was conducted in MEDLINE (via PubMed), Embase, and The Cochrane Central Register of Controlled Trials (CENTRAL), for studies published up until October 25 2021. The following search terms were used in all databases: (injection OR steroid OR methylprednisolone OR betamethasone OR triamcinolone OR lidocaine OR NSAID OR saline OR 'sodium chloride' OR corticosteroid OR conservative OR PRP OR 'platelet rich plasma' OR 'stem cell' OR collagen OR hyalur*OR prolotherapy). There was no restriction applied to the search. Reference lists of the included studies were screened for additional eligible articles.

#### 7.1.2. Eligibility Criteria

The yield of the search was combined in a reference manager software (EndNote X9; Clarivate Analytics, Philadelphia, Pennsylvania). After the automatic and manual removal of duplicate records, two independent authors evaluated the title, abstract and full text of all studies. First, we performed a primary selection based on title and abstract simultaneously, then we assessed full-texts for inclusion. A third author resolved disagreements. We used the PICO framework to assess study. We included only randomized controlled trials (RCTs) that investigated patients having partial rotator cuff tear (P), and compared different injection therapies (I: hyaluronic acid, platelet rich

plasma, adipose-derived regenerative cells, saline injections, C: steroid injection). The outcomes (O) we examined were clinical scores like Visual Analogue Scale (VAS), Constant-Murley Shoulder Outcome Score (CMS), and American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form (ASES) [45, 46]. We examined the change in these clinical scores from baseline (immediately before receiving the injection). VAS scores were examined at week 0, week 4, and 6 months post-intervention. A better outcome was associated with a lower score. CMS was assessed at baseline and at 3 and 6 months. The ASES score was compared with the baseline score at 6 and 7 months. CMS and also ASES were both more favorable with a higher score. Partial tears were confirmed by MRI scans in all cases. Studies were included if the partial rotator cuff tear was isolated, was not a full-thickness tear and was not associated with other pathology. Abstracts and grey literature (preprints and other non-peer-reviewed material) were excluded from the analysis.

### 7.1.3. Data Extraction

Two independent review authors extracted data in duplicate into a standardized data collection form (Microsoft Excel 365, Microsoft Corporation, Redmond, Washington). Disagreements were resolved by consensus. We used a standardized data collection sheet to collect all the necessary data: first author, publication year, study design, clinical outcome (dependent variable) was measured using the VAS for pain assessment ranging from 0 (best, i.e. no pain) to 10 (worst, i.e. extreme pain); the ASES ranging from 0 (worst) to 100 (best) (it consists of two dimensions: pain and activities of daily living); and the CMS with both subjective and objective components ranging from 0 (worst) to 100 (best); and the means, standard deviations, medians, ranges, and interquartile ranges related to clinical scores. The authors of the eligible articles were not contacted for further information.

### 7.1.4. Statistical analysis

Primary data extraction and organization was carried out in Microsoft Excel. Finally, we analyzed five outcomes: CMS (baseline to 3 months and 0 to 6 (in one case 7) months)), VAS (baseline to 4 weeks and 0 to 6 months), and ASES (baseline to 6 months). In all cases, the effect size was mean difference (MD) of change from the baseline to the post-intervention score. The mean and standard deviation (SD) of change to baseline values

were extracted from each treatment arm. Often, SD of changes was not directly available. In such cases we used the standard error (SE) or confidence interval (CI) of mean change, or p-value of the paired t-test on the significance of the change. If neither of these were available, the SD of change was calculated from the before (baseline) and after (follow-up) SD values and Pearson's correlation coefficient r. R was imputed from included studies where it was computable [47]. If r could not be computed, we used r = 0 based on the clinical assumption that patient status does not get worse during postoperative follow-up. Method of comparison was frequentist network meta analysis[48]. We applied a random effects approach to pool effect sizes because of considerable between-study heterogeneity of the included articles. Multi-arm study correlation was taken into consideration. Heterogeneity variance was not numerically assessed due to the low number of included studies. Point and interval estimate for each intervention compared to a reference intervention (here: saline) was summarized in forest plots[49]. Treatment effect estimates for all comparisons were summarized in league tables [44]. Netsplit forest plots were used to assess local inconsistency. Reliability of effect size estimates was evaluated by direct evidence plots[48]. Publication bias was not assessed due to the low number of included studies. Treatments were ranked by the P-score ranking metric, which measures the extent of certainty that a treatment is better than another, averaged over all competing treatments [49]. We used the meta[50], netmeta [51], dmetar [52] packages of R [53]. The confidence interval (CI) (1-α) was set to 95%.

### 7.1.5. Risk of Bias Assessment

The risk of bias assessment was performed independently by two authors using the RoB 2 tool for randomized controlled trials recommended by the Cochrane collaboration. Disagreements were resolved by consensus. The following six domains were considered: (i) randomized process, (ii) deviation from intended interventions, (iii) missing outcome data (iv) measurement of the outcome, (v) selection of the reported result, and (vi) overall bias. We used the robvis (see https://mcguinlu.shinyapps.io/robvis/) web app tool to visualize the risk of bias assessment [54].

### 7.1.6. Certainty of Evidence

The Grading of Recommendations Assessment, Development and Evaluation Working Group modality (GRADE) approach was used to assess certainty of evidence [55]. The

certainty of evidence was independently assessed by two authors, disagreements were resolved by consensus.

## 7.2.Study II.

### 7.2.1. Search strategy

A systematic search was conducted in MEDLINE (via PubMed), Embase, and The Cochrane Central Register of Controlled Trials (CENTRAL), for studies published until October 20022. The following search terms were used in all databases: 'shoulder' AND (Cutibacterium OR Cutibacter OR Propioni* OR 'C. acnes' OR 'P. acnes' OR acnes) AND (hydrogen OR hyperol OR HP OR H2O2 OR benzoyl OR benzil OR 'benzoyl-peroxide'). No restrictions were applied during the search. In addition, the reference lists of the included studies were screened for additional eligible articles.

### 7.2.2. Eligibility criteria

The yield of the search was combined with reference manager software (EndNote X9; Clarivate Analytics, Philadelphia, Pennsylvania). After the automatic and manual removal of duplicate records, two independent authors evaluated all studies' titles, abstracts, and full texts. First, we simultaneously performed a primary selection based on the title and abstract. Then we assessed full texts for inclusion. We used the PICO framework to assess study eligibility. We included only randomized controlled trials (RCTs) that investigated patients' shoulder skin (P) and that compared different skin preparations (hydrogen peroxide – H2O2), 5% benzoyl peroxide – BPO 5%, 5% benzoyl peroxide with clindamycin – BPO 5% CLI, 5% benzoyl peroxide with miconazole-Nitrate – BPO 5% CLI MN), 10% benzoyl peroxide – BPO 10%, 3% hexachlorophene – pHisohex, chlorhexidine gluconate – CHG, control). The outcomes (O) we examined were the reduced *C. acnes* culture in skin swabs, dermis swabs, and joint culture. Our study compared alcohol-based skin preparation with alcohol-based skin preparation supplemented with peroxide solutions. If there was less *C. acnes* outgrowth after skin treatment, this was considered a more favorable outcome. After sampling, the bacteria were cultured in anaerobic conditions for at least 12 days. Abstracts and grey literature (preprints and other non-peer-reviewed material) were excluded from the analysis.

### 7.2.3. Data extraction

Two independent review authors extracted data in duplicate into a standardized data collection form (Microsoft Excel 365, Microsoft Corporation, Redmond, Washington). We used a standardized data collection sheet to collect all the necessary data: first author;

publication year; study design; the clinical outcome was the skin dermis, and the joint culture after peroxide solution compared with the control group. A third party resolved discrepancies. The authors of the eligible articles were not contacted for further information.

### 7.2.4. Statistical analysis

We performed a frequentist network meta-analysis from the acquired data comparing multiple interventions with the control. all cases, the effect size was risk ratio (RRs) with 95% confidence intervals (CIs) [49]. We applied a random effects approach to pool effect sizes because of the considerable between-study heterogeneity of the included articles. Multi-arm study correlation was taken into consideration. Heterogeneity variance was not numerically assessed due to the low number of included studies. Point and interval estimate for each intervention compared to a reference intervention (here: none) was summarized in forest plots [50]. Treatment effect estimates for all comparisons were summarized in league tables [44]. Netsplit forest plots were used to assess local inconsistency. The reliability of effect size estimates was evaluated by direct evidence plots [48]. Publication bias was not assessed due to the low number of included studies. Treatments were ranked by the P-score ranking metric, which measures the extent of certainty that a treatment is better than another treatment, averaged over all competing treatments [51]. The confidence level (1-α) was set to 95%.

### 7.2.5. Risk of bias assessment

The risk of bias assessment was performed independently by two authors (VW and BH) using the Risk of Bias (RoB) 2 tool for RCTs recommended by the Cochrane Collaboration. Disagreements were resolved by consensus. We used the Robvis web app tool to visualize the risk of bias assessment [54].

### 7.2.6. Certainty of evidence

The Grading of Recommendations Assessment, Development and Evaluation Working Group modality (GRADE) approach was used to assess the certainty of evidence. The certainty of the evidence was independently assessed by two authors and disagreements were resolved by consensus [55].

# 8. RESULTS

## 8.1.Study I

### 8.1.1. Results of search and selection

A total of 7,512 records were identified through an electronic database search, of which seven publications were included [23-29]. The detailed selection process is described in the PRISMA flow diagram (Figure 1).

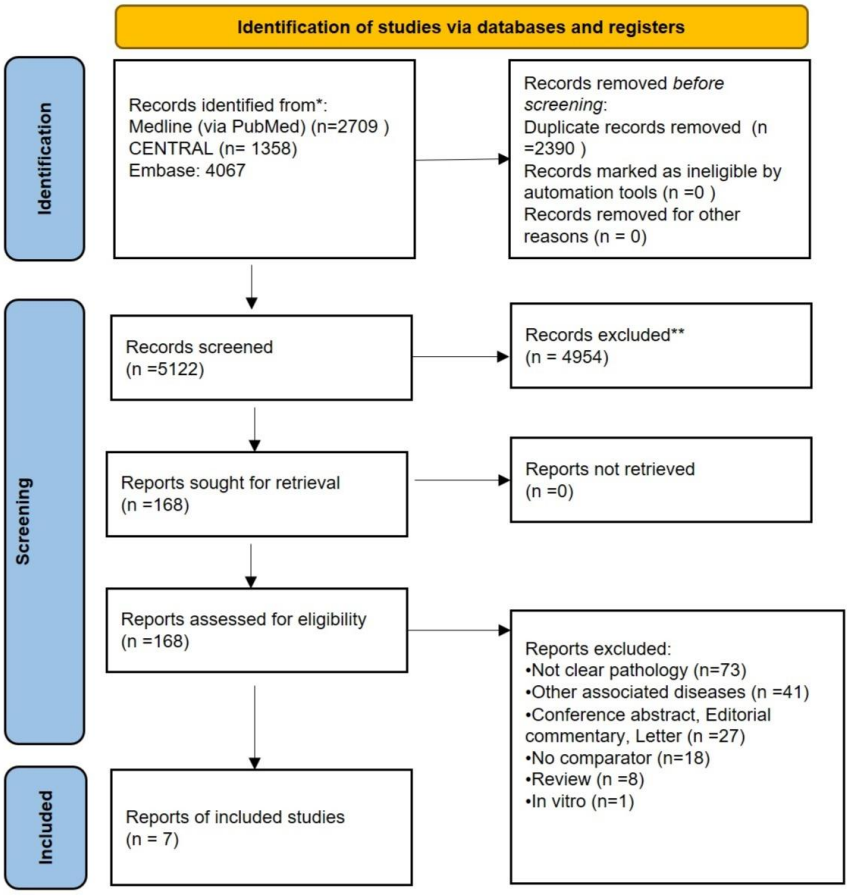



**Figure 1.** PRISMA 2020 Flowchart representing the study selection process

### 8.1.2. Characteristics of the studies included

All included studies were single-center randomized controlled trials (RCTs). Of the seven studies, two compared HA with saline as a placebo [23, 24]. One study compared HA with saline, PRP, and a combination of HA with PRP [26]. Two different studies compared PRP with steroid therapy[25, 29], one study compared PRP with saline [27], and one study compared uncultured, unmodified, autologous adipose-derived regenerative cells (UA-ADRCs) with steroid therapy [28]. The detailed description of the included studies is shown in Table 1. The network graph of the included publications' interventions is presented in Figure 2.

**Table 1.** Characteristics of included studies

| Author, year, country, number of centers | N0 of patients (age, N0 of females) | Inclusion criteria | Exclusion criteria | Intervention | Event number: | Outcomes |
|---|---|---|---|---|---|---|
| Wen-Yi Chou[23] et al., 2010, Taiwan | 51 patients (median age NA, 32) | patients who had pain around the shoulder, a positive impingement sign, rotator cuff pathology without a complete tear; not respond to conservative therapy at least 3 months; between 35 and 80 years | rheumatic diseases, glenohumeral osteoarthritis, full-thickness cuff tears, fractures, infections, or tumors, hypersensitivity to hyaluronate, participated in any other study within 3 months; who had received a subacromial injection within 3 weeks; pregnant or wanted to become pregnant | Hyaluronic acid vs Saline<br>HA: ARTZ Dispo, 25 mg of SH<br>Placebo : 0.9% normal saline solution, at 2.5 mL/syringe, in the same package | 25 vs 26 | CMS, VAS score, global tolerability assessed by the physician Week 1-2-3-4-5-6-12 |
| Alireza Moghtaderi et al. [24], 2013, Iran | 40 (N/A,N/A) | between 30 and 80 years, a positive Neer and Hawkins sign, and a positive ultrasonographic diagnosis without a complete tear, did not respond to conservative treatments at least 6 months | rheumatic disease, glenohumeral osteoarthritis, full-thickness tears, fractures, diabetes mellitus, infections, or tumors, had hypersensitivity to hyaluronate, had participated in any other study within 6 months, subacromial injection within 8 weeks, pregnant, were at risk of complications of intra-articular injections such as patients who received anti-coagulant | HA vs. Saline<br>Fermathron™, 20 mg/2 ml of sodium hyaluronate. The placebo was 0.9% normal saline solution, at 2 mL/syringe. Both groups received 3 weekly injections in a same protocol. | 20 vs 20 | CMS, VAS score 1-2-3-12 weeks after treatment |
| Ahmed Shams et al.[25], 2016, Egypt | 40 patients (mean age 51±11years, 19fm) | MRI evidence of a partial supraspinatus tear. | generalized inflammatory arthritis, infection, osteoarthritis of the shoulder, nerve-related symptoms, known malignancy and bleeding disorders. | PRP vs. Steroid<br>PRP: aspirated with citrate dextrose anticoagulant, it was centrifuged at 3500 RPM for 10 min. Upper 4 ml, which | 20 vs 20 | 6, 12 weeks, 6 months: ASES, CMS, SST, VAS 6months after the intervention MRI |

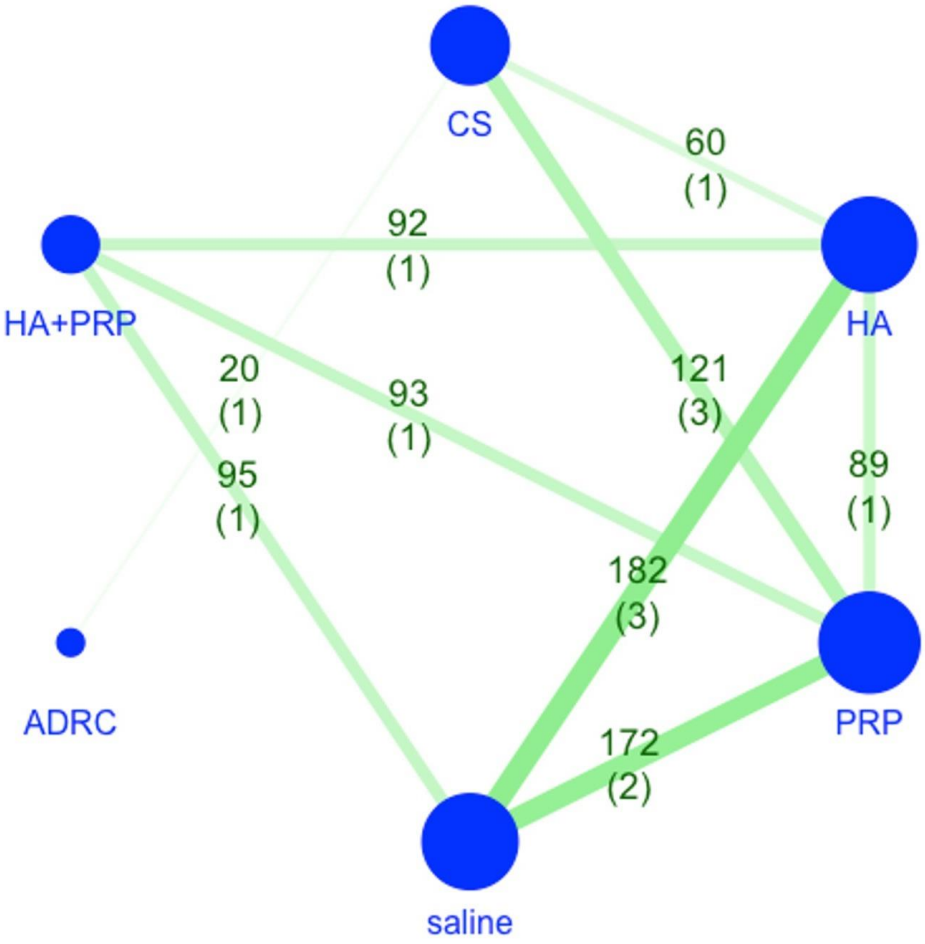
| Author, year, country, number of centers | N0 of patients (age, N0 of females) | Inclusion criteria | Exclusion criteria | Intervention | Event number: | Outcomes |
|---|---|---|---|---|---|---|
| | | | | represents the platelet-poor plasma (PPP) phase, was discarded. The remaining above the gel was the platelet-rich plasma (PRP) phase. Corticosteroid injection : Kenacort-A 40 mg, (triamcinolone) | | grade |
| Yu Cai et al[26]., 2018, China | 184 patients (mean age NA, 85) | PTRCT diagnosed by clinical examination and magnetic resonance imaging (MRI) | Elderly patient > 60 years, RC tears secondary to fracture, prior operation, prior other drug intervention, pregnant, shoulder pain induced by non RC tear, active infection, Haemoglobin < 7.0 g/dl or platelet < 15,000/nL | Saline vs HA vs PRP vs HA+PRP Saline: 4 mL of Saline Hyaluronate: 4 mL of HA PRP: (20 mL) collected from each patient was injected into an anticoagulant tube centrifuged at 4-C for 10 min at 1500 rpm.), SH+PRP group was treated with 2 mL of PRP and 2 mL of SH. | 47 vs 44 vs 45 vs 48 | CMS, American Shoulder and Elbow Surgeons (ASES) and the VAS scores. 1-3-6-12 months |
| Adrien J. Schwitzguebel et al.[27] 2019, Switzerland | 80 adults, NA, 35fm | interstitial supraspinatus tear | concomitant tendon tears; a frozen shoulder, defined as a restriction of 20% in external rotation as well as active and passive elevation, shoulder steroid infiltrations past 3 months; calcifying tendinopathies | PRP vs. Saline PRP: centrifugation for 5 minutes at 1500 revolutions per minute, collection of 2 mL of the platelet-rich supernatant Saline: saline solution | 41 vs 39 | 7 months after the intervention: lesion volume, calculated on MRA, VAS, SANE, CMS, ASES, Adverse events, additional treatments after 7 months 12 months follow up with VAS |

| Author, year, country, number of centers | N0 of patients (age, N0 of females) | Inclusion criteria | Exclusion criteria | Intervention | Event number: | Outcomes |
|---|---|---|---|---|---|---|
| | | | | | | and SANE |
| Jason L. Hurd et al.[28], 2020, USA | 16 patients (mean age NA, 3) | radiologists and the treating orthopedic shoulder specialist, and had to correlate with findings from clinical examination to come to the diagnosis of PTRCT. | Full-thickness tear, Insufficient amount of subcutaneous tissue, Malignancy, Immunosuppressant therapy, received a corticosteroid injection in last 3 months, severe arthrosis, fatty atrophy, previous surgeries, tobacco use, liver disease or an alanine aminotransferase value >400, allergy to sodium citrate,pregnancy | UA-ADRCs vs. Steroid UA-ADRCs: 11.4 × 106 UA-ADRCs in 5 mL liquid corticosteroid : 80 mg of methylprednisolone plus 3 mL of 0.25% bupivacaine | 11 vs 5 | ASES score, RAND score, VAS score, size of the PTRCT, compared to baseline. Week 3, W6, W9, W12, W24, W32, W40, and W52 post treatment; MRI scans were performed at BL, W24, and W52 post treatment. |
| Marvin Thepsoparn et al.[29], 2021, Thailand | 31 patients (mean age NA, 25) | 18 and 80 years and no serious systemic diseases, partial supraspinatus tendon tears, natural history of tears from repetitive trauma or overuse only. Failed physical therapy and oral medication for at least 3 | Severe arthritis or other complications related to supraspinatus tears, previous shoulder surgery. Other concurrent shoulder conditions such as impingement. Malignancy. Current treatment using anticoagulant or antiplatelet medication Immunocompromised | PRP vs Steroid PRP: centrifuged at 1500 rpm for 5 minutesthe corticosteroid group, 1 mL of triamcinolone acetonide (40 mg/mL Kenacort-with 4 mL of 1% lidocaine) | 15 vs 16 | 1 month, 6 months VAS, OSS Score |

| Author, year, country, number of centers | N0 of patients (age, N0 of females) | Inclusion criteria | Exclusion criteria | Intervention | Event numbe r: | Outcomes |
|---|---|---|---|---|---|---|
| | | months. Ability to participate for a minimum follow-up period of 6 months. | status | | | |

ASES, American Shoulder and Elbow Surgeons; BL, baseline; CMS, Constant-Murley Shoulder Outcome Score; fm, female; HA, hyaluronic acid; MRA, magnetic resonance arthrogram; MRI, magnetic resonance imaging; NA, not available; OSS, Oxford Shoulder Score; PRP, platelet-rich plasma; PTRCT, partial-thickness rotator cuff tear; RAND, RAND 36-Item Short Form Survey; RC, rotator cuff; rpm, revolutions per minute; SH, sodium hyaluronate; SANE, Single Assessment Numeric Evaluation; SST, simple shoulder test; UA-ASRC, uncultured, unmodi ed, autologous adipose-derived regenerative cell; VAS, visual analog scale.

**Figure 2.** Network Graph of the included interventions



### 8.1.3. Outcomes

8.1.3.1.Visual Analogue Scale (VAS) (0-4 weeks)

Three studies with 266 participants and five intervention categories contributed to the network meta-analysis (NMA) assessing VAS 0-4 weeks [23, 26, 29]. HA contributed 25.9 % of the data, saline 27.4%, PRP 22.5%, steroid 6.0%, and PRP+HA the remaining 18.0%. Combination of HA and PRP (HA+PRP MD=−0.99, [CI = −1.62, −0.36]; HA MD=−0.43, [CI = −1.01, 0.14]; PRP MD=−0.17, [CI = −0.73, 0.40], and steroid MD=0.43, [CI = −1.50, 2.36]) was the most effective in decreasing VAS score in the first 4 weeks compared to saline. Interestingly, steroid seemed to be the least effective. However, the difference was non-significant compared to saline. HA+PRP had the highest likelihood of achieving VAS score decreasing considering both direct and indirect comparison. Using rank plot, HA+PRP (P score: 0.966) proved to be the most effective treatment followed by HA (P score: 0.648) and PRP (P score: 0.416) alone, then saline (P score: 0.254), and steroid (P score: 0.216) as the least effective (Figure 3) agent.

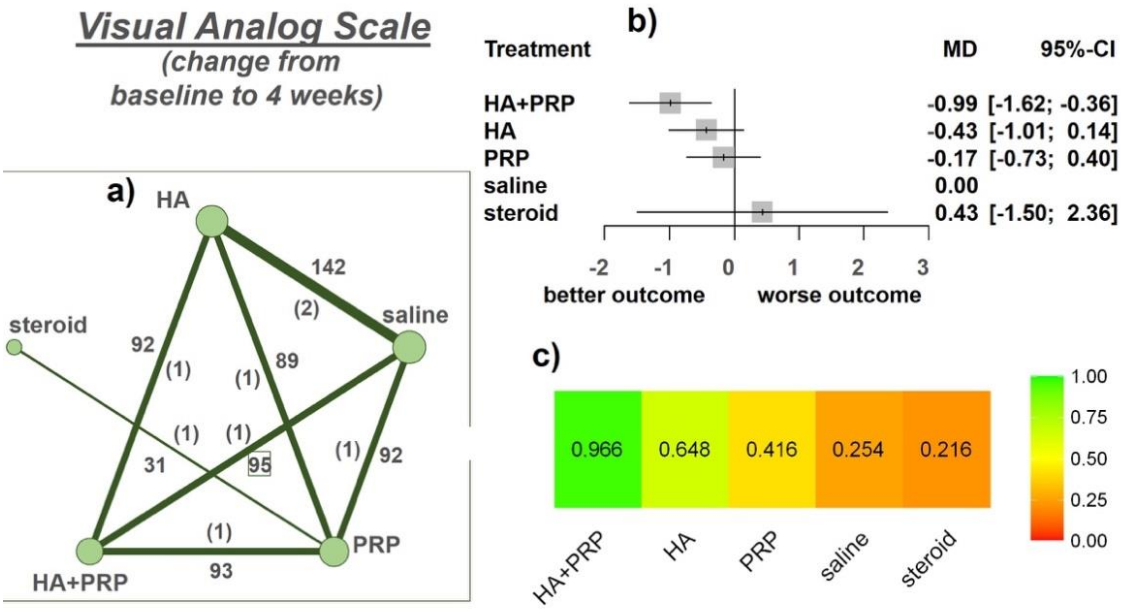



**Figure 3.** Summary figure for the change between baseline and 4 weeks in pain measured using the visual analog scale.
(CI, confidence interval; HA, hyaluronic acid; MD, mean difference; PRP, platelet-rich plasma.)

8.1.3.2.Visual Analogue Scale (VAS) (0-6 months)

Four studies with 312 participants and six intervention categories contributed to the NMA assessing VAS after 6 months [26-29]. PRP contributed 32.3 % of the data, saline 27.9 %, HA+PRP 15.4 %, HA 14.1 %, steroid 6,7 % and ADRC the remaining 3,5 %. Combination of HA and PRP (HA+PRP MD=−3.00 [CI = −6.09, 0,08]; HAMD= −1.59 [CI = −4.69, 1.51]; PRP MD=−1.59 [CI = −3.97, 0.79], ADRC MD=-0.88 [CI = -7.07, 5.31]; steroid: MD=0.91 [CI = −3.45, 5.26]) was the most effective in decreasing VAS score 6 months after the intervention compared with saline, however our results are statistically not significant. Using rank plot we can say that the most effective treatment was HA+PRP (P score: 0.854) followed by HA (P score: 0.619), PRP (P score: 0.595), and ADRC (P score: 0.496), then saline (P score: 0.266), and steroid (P score: 0.170) as the least effective (Figure 4) method.

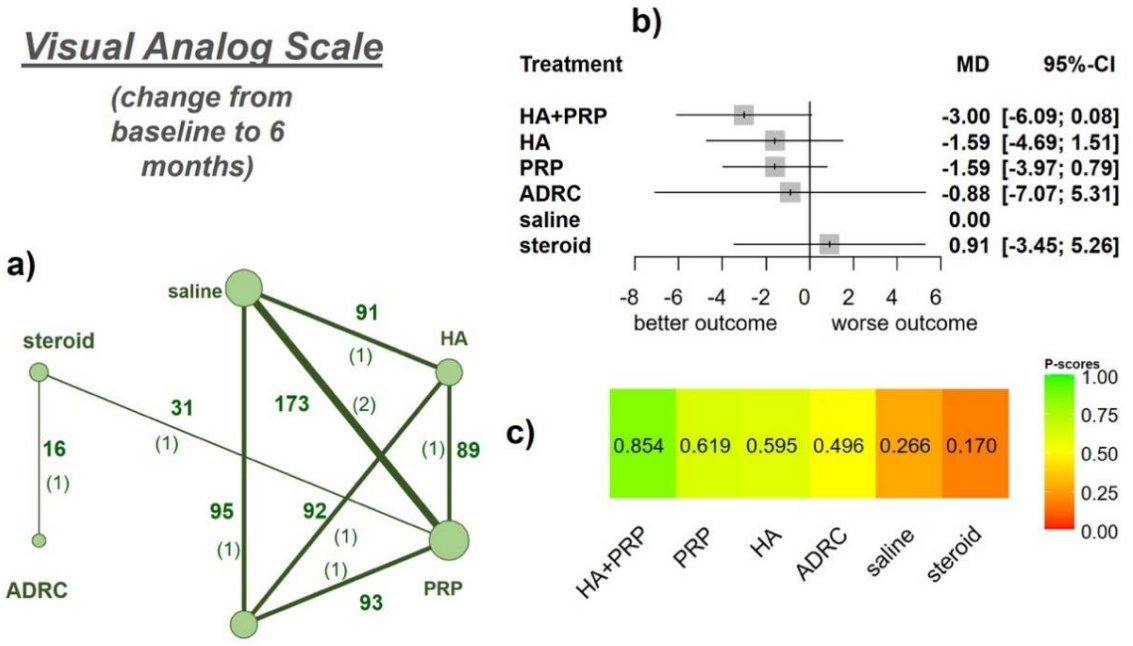



**Figure 4.** Summary figure for the change between baseline and 6 months in pain measured using the visual analog scale. (ADRC, adipose-derived regenerative cell; CI, confidence interval; HA, hyaluronic acid; MD, mean difference; PRP, platelet-rich plasma.)

8.1.3.3.Constant-Murley score (CMS) (0-3 months)

Four studies with 315 participants and five intervention categories contributed to the NMA assessing Constant Murley Score from 0 to 3months [23-26]. PRP contributed 34.7 % of the data, saline 28.5%, HA+PRP 15.7%, HA 14.4%, and steroid the remaining 6.7%. Combination of HA and PRP (HA+PRP MD=20.56 [CI = 16.18, 24.94]; HA MD=14.95 [CI = 11.05, 18.86]; PRP MD=11.82 [CI = 7.40, 16.24], steroid MD=-5.38 [CI = −18.10, 7.34]) provided the best results in increasing the CMS in the first 3 months compared to saline. Using rank plot it was found that the best treatment was HA+PRP (P score: 0.999) followed by HA (P score: 0.732) and PRP (P score: 0.519), then saline (P score: 0.199), and steroid (P score: 0.052). (Figure 5)

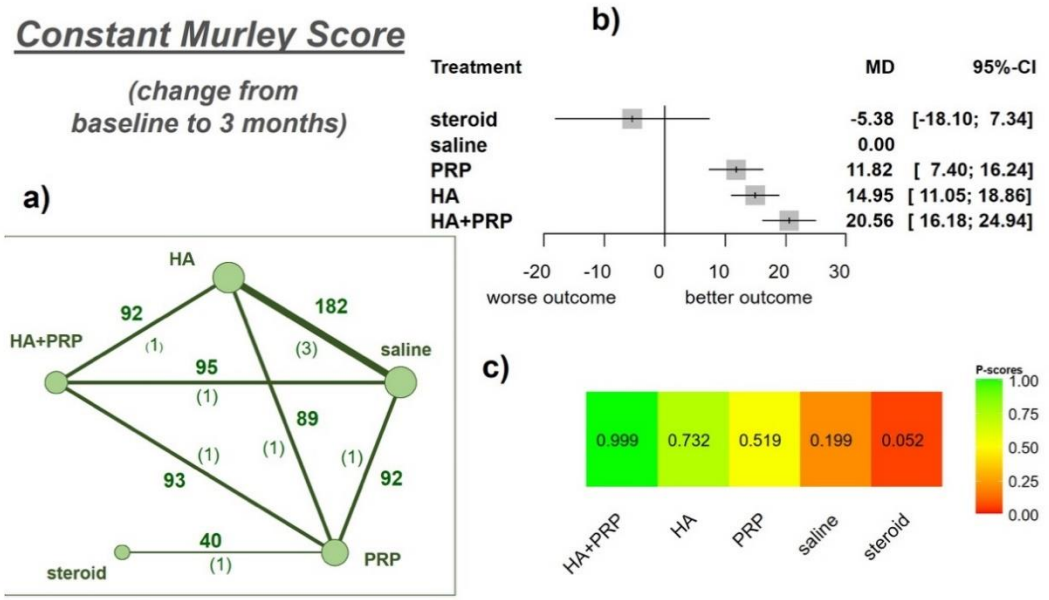



**Figure 5.** Summary figure for Constant-Murley Shoulder Outcome Score changes from baseline to 3 months. (CI, confidence interval; HA, hyaluronic acid; MD, mean difference; PRP, platelet-rich plasma.)

8.1.3.4.Constant-Murley score (CMS) (0-6 months)

Three studies with 305 participants and five intervention categories contributed to the NMA assessing Constant Murley Score 0 to 6 months [25-27]. PRP contributed 34.7 % of the data, saline 28.5%, HA+PRP 15.7%, HA 14.4%, and steroid the remaining 6.7%. Combination of HA and PRP (HA+PRP MD=23.40 [CI = -3.00, 49.79]; PRP MD=8.50 [CI = -11.71, 28.71], HA MD=6.74 [CI = -19.67, 33.15]; steroid MD=1.60 [CI = −35.41, 38.60]) showed the most promising result in increasing the CMS in the first 6 months compared to saline. Saline was the least effective. The difference between saline and the other interventions were not significant. Using rank plot the most effective treatment was HA+PRP (P score: 0.889) followed by PRP (P score: 0.537) HA (P score: 0.465), and steroid (P score: 0.354) (Figure 6).

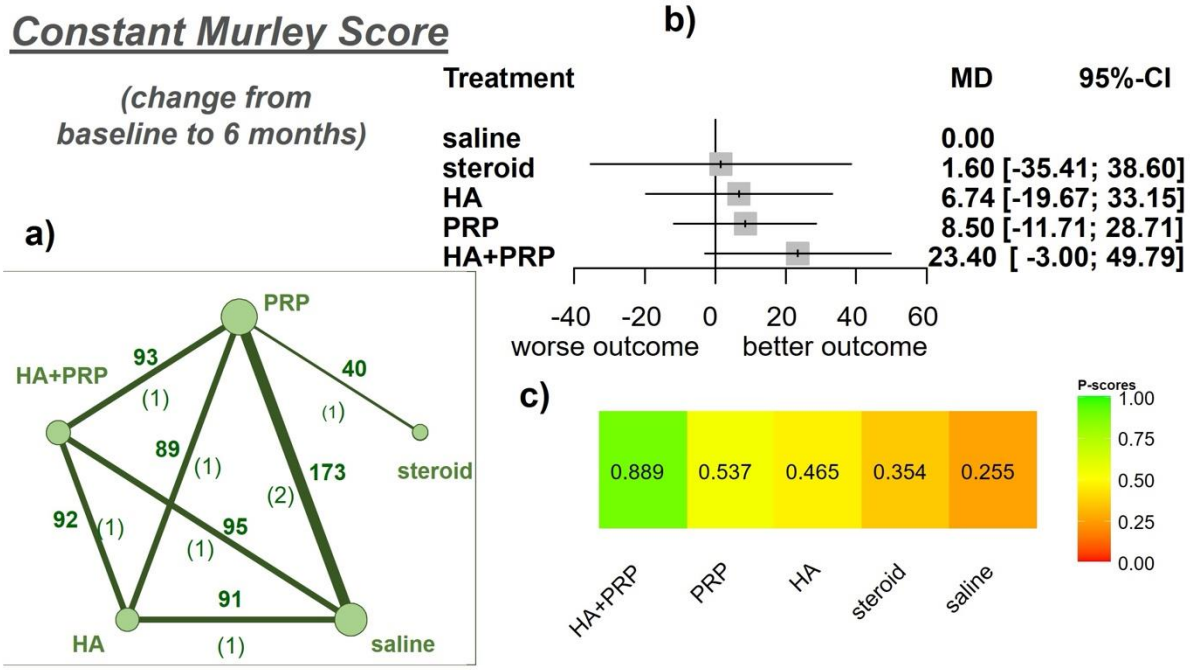



**Figure 6.** Summary figure for Constant-Murley Shoulder Outcome Score changes from baseline to 6 months. (CI, confidence interval; HA, hyaluronic acid; MD, mean difference; PRP, platelet-rich plasma.)

8.1.3.5.American Shoulder and Elbow Surgeons (ASES) Score (0-6 months)

Three studies with 305 participants and five intervention categories contributed to the NMA assessing ASES Score 0 to 6 months [25-27]. PRP contributed 34.7 % of the data, saline 28.5%, HA+PRP 15.7%, HA 14.4%, and steroid the remaining 6.7%. Combination of HA and PRP (HA+PRP MD=28.02 [CI = -0.50, 56.55]; PRP MD=9.44 [CI = -12.64, 31.51], HA MD=6.80 [CI = -21.77, 35.37]; steroid MD=5.04 [CI = −33.48, 43.55]) appeared to be the most effective injection therapy in increasing the ASES-score half year after the initial intervention. Saline and steroid were the least effective. The difference between saline and other agents was not significant. Using rank plot we can say that the most effective treatment was HA+PRP (P score: 0.910) followed by PRP (P score: 0.520), HA (P score: 0.432), steroid (P score: 0.401), and the saline (P score: 0.237) (Figure 7).

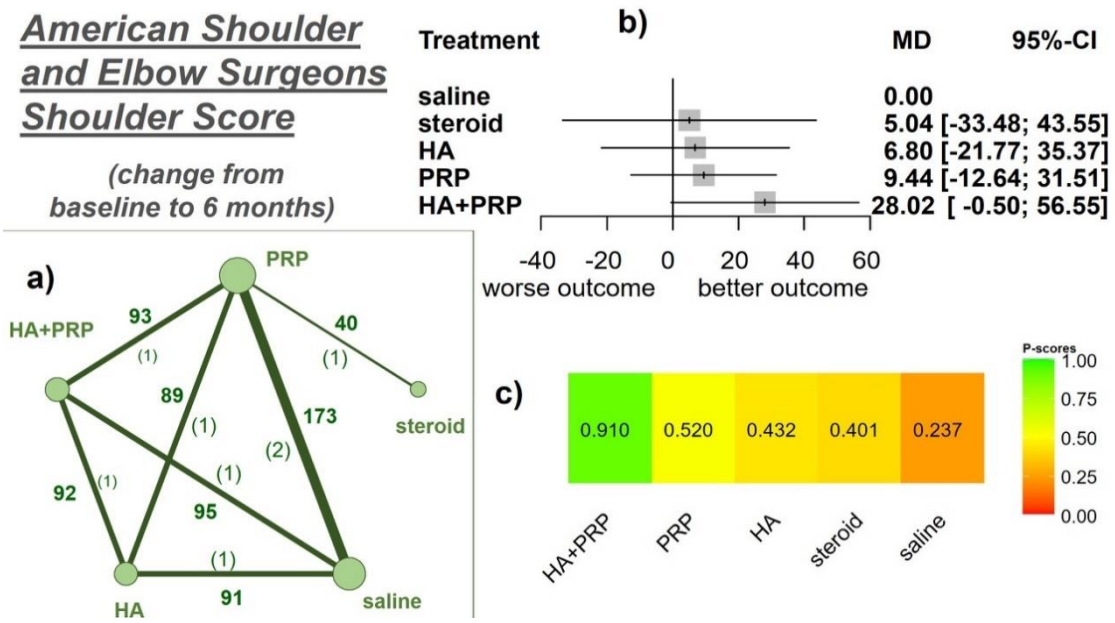



**Figure 7.** Summary figure for American Shoulder and Elbow Surgeons score changes from baseline to 6 months. (CI, confidence interval; HA, hyaluronic acid; MD, mean difference; PRP, platelet-rich plasma.)

### 8.1.4. Risk of bias assessment and certainty of evidence

Most of the included articles were judged as "low" to moderate ("some concerns") risk of bias, except one article, which had high risk of bias (due to "bias in measurement in outcome"). The quality of evidence in the studies was variable. The grade of evidence was of moderate or very low quality for each pairwise comparison between interventions.

## 8.2.Study II

### 8.2.1. Result of search and selection

A total of 214 records were identified through electronic database searches, of which ten publications were included in our network meta-analysis (Figure 8) [31-33, 35-39, 56, 57].

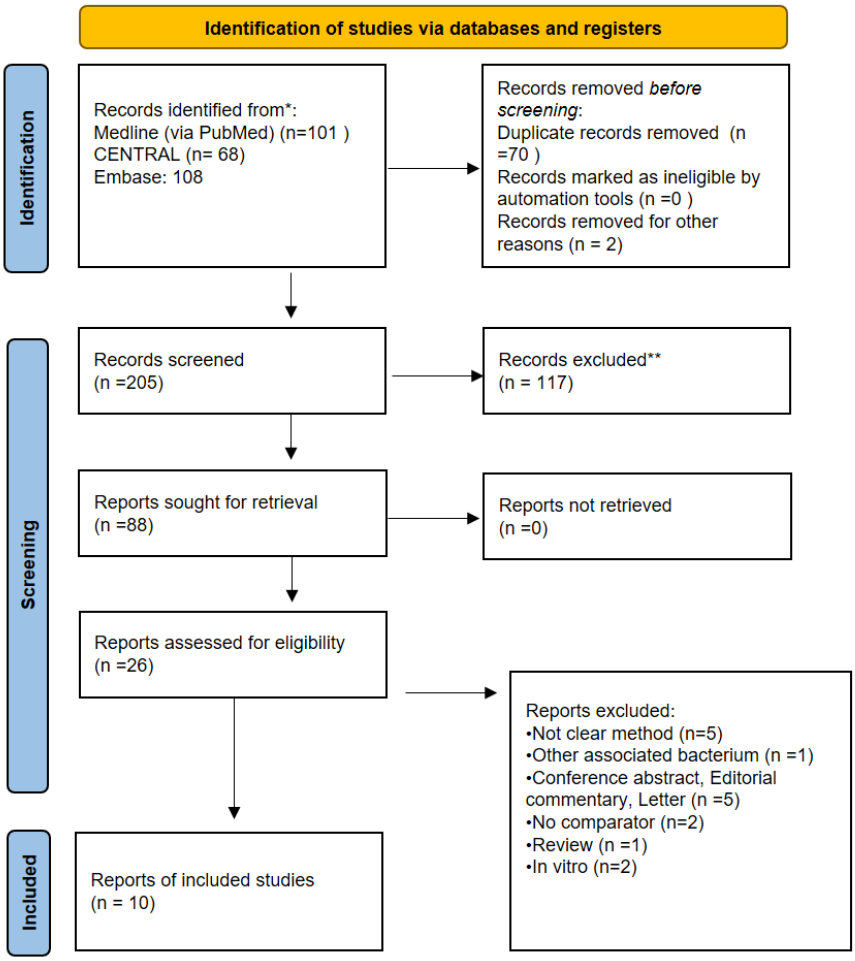



**Figure 8.** PRISMA 2020 Flowchart representing the study selection process

### 8.2.2. Characteristics of the studies included

All included studies were single-center randomized controlled trials (RCTs). Two of the ten articles compared the H2O2 with 4% CHG [31, 32]. One of them compared the 10% BPO with 4% CHG[33], and tree compared 5% BPO with the 4% CHG [35, 36, 56]. One

article compared the 5% BPO with regular soap[57]. One article compared the 5% BPO with phisohex  and 5% BPO+Clindamycin[37] . One article used 5% BPO plus MN [38], and one compared the 5% BPO with placebo [39].  A detailed description of the included studies is shown in Table 2.

**Table 2.** Basic characteristics of included studies

| Author (year) | Study site | No patients (Male %) | Shoulder intervention indication | Intervention | Control | Outcomes Skin/dermis/joint | Germ count |
|---|---|---|---|---|---|---|---|
| Grewal G 2021[31] | USA | 60(48) | primary arthroplasty | hydrogen peroxide | standard skin preparation | Culture samples | positive culture or not |
| Hancock D 2018 [35] | New Zealand | 22 (100) | non-surgery, healthy volunteers | benzoyl peroxide | 2% chlorhexidin and alcohol | Prior to skin preparation two swabs were taken from each shoulder region | positive culture |
| Hsu EJ 2020 [33] | USA | 50 (100) | shoulder arthroplasty | 10% benzoyl peroxide soap (BPO group) | 4% chlorhexidine gluconate solution (CHG group) | skin surface swab, dermal edge swab | positive culture, Specimen Cutibacterium Value (SpCuV) |
| Kolakowski 2018 [56] | USA | 80(46) | primary or revision shoulder surgery | 5% benzoyl peroxide | 4% chlorhexidine gluconate solution (CHG group) | skin swab at the anterior, lateral, and posterior arthroscopic portal sites and the axilla | positive culture |
| Scheer VM 2018 [36] | Sweden | 40 (60) | non-surgery, healthy volunteers | 5% benzoyl peroxide | 4% chlorhexidine gluconate solution (CHG group) | before and after topical treatment, after surgical skin preparation and sterile draping | positive culture |
| Scheer VM 2021 [57] | Sweden | 100(63) | primary elective open shoulder surgery | 5% benzoyl peroxide | CHG | after surgical skin preparation, 1 in dermis, and finally after the skin was sutured. Before skin incision, 5 punch biopsies | positive culture |

| Author (year) | Study site | No patients (Male %) | Shoulder intervention indication | Intervention | Control | Outcomes Skin/dermis/joint | Germ count |
|---|---|---|---|---|---|---|---|
| Stull DJ 2019 [32] | USA | 70(100) | shoulder arthroscopy | additional with 3% hydrogen peroxide | standard skin preparation | 3-mm punch biopsy was obtained from the posterior arthroscopic portal site of all patients | positive culture |
| Symonds T 2022 [37] | Australia | 101(60) | total shoulder arthroplasty | BPO/BPO+C | Phisohex solution | Swab1-skin, Swab2-skin, Swab3-dermis, Swab4-joint, Swab5-dermis, Swab6-surgic. trolley | positive culture |
| Unterfrauner I 2021 [38] | Switzerland | 60(45) | open shoulder surgery | 5% BPO/ 2%MN | standard skin preparation | Swab1-skin, Swab2-skin, Swab3-subcutaneous Swab4-capsule | positive culture |
| Van Diek FM 2020 [39] | Netherland | 29 | healthy participants | 5% benzoyl peroxide | placebo | Skin | positive culture |

**‡ parameters represented as mean with standard deviation, or median with range (minimum and maximum)**

BPO: Benzoil peroxide, BPO+C: Benzoil peroxide plus Clindamycin, MN: Miconasole Nitrate, CHG: Chlorhexidine

The network graph of the included publications' interventions is presented in Figure 9. Our network meta-analysis compared the *C. acnes* reduction potential of different interventions. We considered the reducing effect of skin flora in our analysis. We did not have enough data on the dermis and articular bacterial flora to perform the analysis.

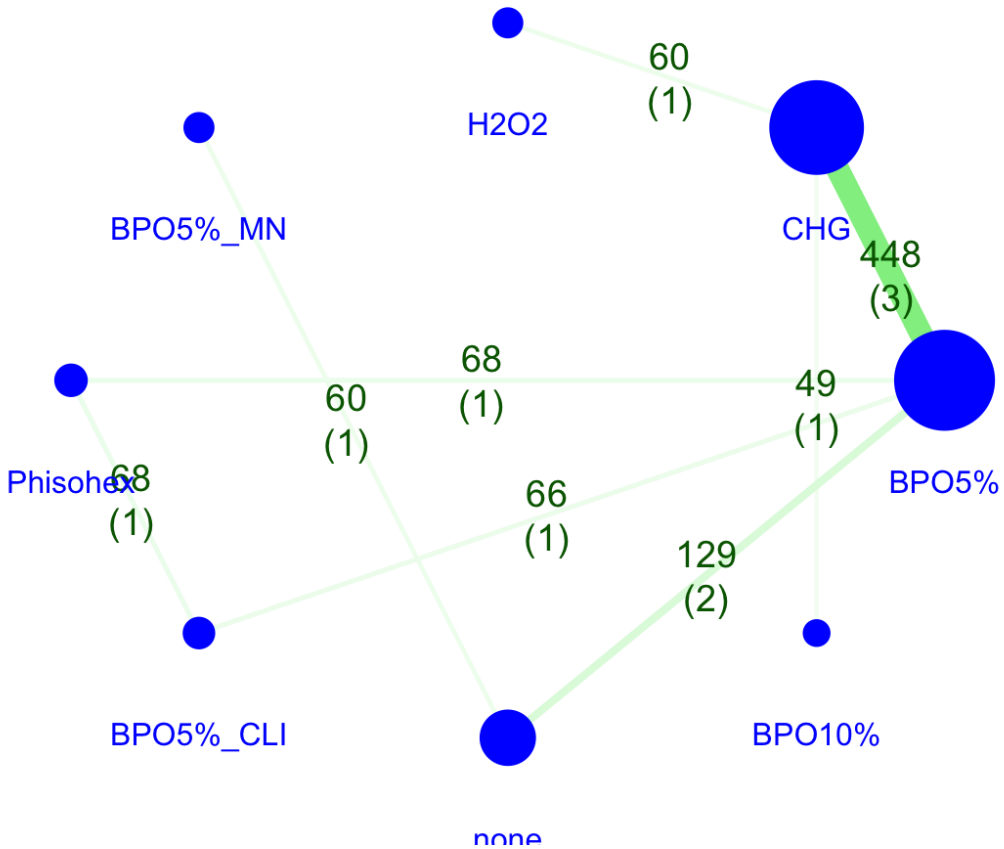



**Figure 9.** Network graph of the included studies

### 8.2.3. Outcomes

8.2.3.1.Effectiveness of different interventions to eradicate *C. acnes* on the skin

In our network meta-analysis, we compared seven different interventions from 10 different articles. In total, we examined 948 intervention events. Figure 9 shows the network graph with the total number of interventions, the number of comparisons, and the number of comparative studies. The forest plot (Figure 10) shows that 5% benzyl peroxide was the only intervention with a significant difference compared to the control group (RR=0.25, CI: 0.08-0.72). 5% BPO in addition to Clindamycin, reduced the cutibacterium flora of the skin on the same level. However, the difference was non-significant compared to the control (RR=0.25, CI: 0.04-1.50). 5% BPO with MN showed the smallest difference compared to the control group (RR=0.80, CI: 0.28-2.30). Based on the rank plot (Figure 4), 5% BPO (P score: 0.808) proved to be the most effective treatment, followed by BPO5% plus CLI (P score 0.749).

Based on the league table (Table 3), we could not find any other significant comparison.

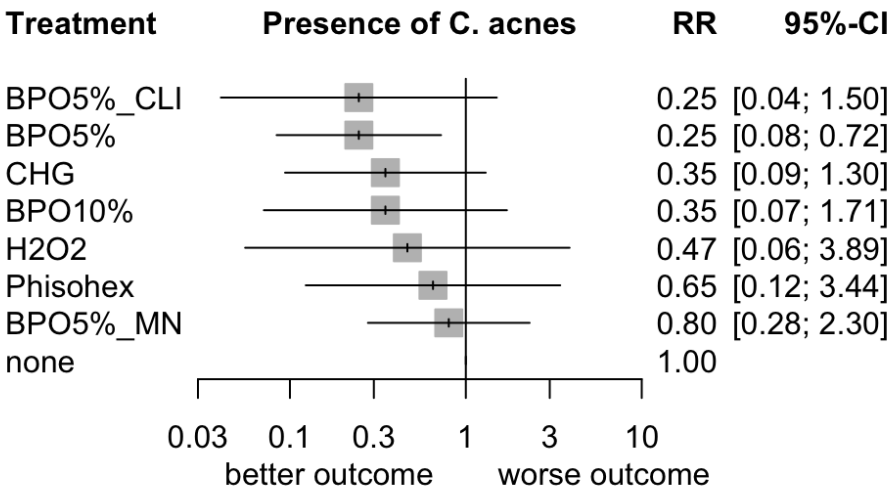



**Figure 10.** Forest plots representing the odds of the positive *C. acnes* culture on skin, BPO: Benzoil peroxide, BPO+CLI: Benzoil peroxide plus Clindamycin, CHG: Chlorhexidine, H2O2: Hydrogen Peroxide, MN: Miconasole Nitrate

**Table 3.** League table

| V1 | V2 | V3 | V4 | V5 | V6 | V7 | V8 |
|---|---|---|---|---|---|---|---|
| **BPO10%** | . | . | . | 1.00 (0.41; 2.45) | . | . | . |
| 1.42 (0.44; 4.57) | **BPO5%** | 1.00 (0.23; 4.26) | . | 0.71 (0.33; 1.50) | . | 0.25 (0.08; 0.72) | 0.38 (0.11; 1.35) |
| 1.42 (0.22; 9.13) | 1.00 (0.23; 4.26) | **BPO5% CLI** | . | . | . | . | 0.38 (0.11; 1.35) |
| 0.44 (0.06; 2.95) | 0.31 (0.07; 1.39) | 0.31 (0.04; 2.50) | **BPO5% MN** | . | . | 0.80 (0.28; 2.30) | . |
| 1.00 (0.41; 2.45) | 0.71 (0.33; 1.50) | 0.71 (0.14; 3.62) | 2.29 (0.42; 12.38) | **CHG** | 0.75 (0.14; 3.98) | . | . |
| 0.75 (0.11; 4.99) | 0.53 (0.08; 3.30) | 0.53 (0.05; 5.47) | 1.72 (0.16; 18.44) | 0.75 (0.14; 3.98) | **H2O2** | . | . |
| 0.35 (0.07; 1.71) | 0.25 (0.08; 0.72) | 0.25 (0.04; 1.50) | 0.80 (0.28; 2.30) | 0.35 (0.09; 1.30) | 0.47 (0.06; 3.89) | **None** | . |
| 0.54 (0.10; 3.02) | 0.38 (0.11; 1.35) | 0.38 (0.11; 1.35) | 1.23 (0.17; 8.84) | 0.54 (0.12; 2.35) | 0.72 (0.08; 6.64) | 1.54 (0.29; 8.13) | **Phisohex** |

Treatment effect estimates for all comparisons were summarized in league tables. BPO: Benzoil peroxide, BPO+CLI: Benzoil peroxide plus Clindamycin, CHG: Chlorhexidine, H2O2: Hydrogen Peroxide, MN: Miconasole Nitrate

8.2.3.2.Effectiveness of different interventions to eradicate *C. acnes* on the dermis

Four articles reported on dermis samples [31, 33, 37, 38]. There was no difference between the H2O2 and control group. When 10% BPO was used as an intervention, it reduced the number of C. acnes cultured in the dermis more than CHG as a control. In the article comparing BPO/BPO+CLI/Phisohex, the best result for reducing dermis *C. acnes* was BPO applied in non-combination, but the combination with CLI also gave better results than the plain phisohex solution. BPO 5% supplemented with 2% MN reduced *C. acnes* better than no intervention ointment.

8.2.3.3.Effectiveness of different interventions to eradicate *C. acnes* in the joint

Three articles dealt with the joint sample [31, 37, 38]. There was no difference in the samples taken for H2O2. In none of the cases did C acnes grew out of the joint. When 5% BPO and 5% BPO+CLI were tested, there were fewer cases of *C. acnes* colonization with these substances than with phisohex solution, but no difference between BPO in combination and BPO alone was found

### 8.2.4. Risk of bias assessment and certainty of the evidence

Most of the included articles were judged as "low" to moderate ("some concerns") risk of bias, except one article, which had a high risk of bias (due to "bias in measurement in outcome"). The grade of evidence was of moderate or very low quality for each pairwise comparison between interventions.

# 9. DISCUSSION

## 9.1.Summary of findings and international comparisons

In the conservative management of PTRCTs, corticosteroids have long been considered the gold standard due to their strong anti-inflammatory properties and relatively low cost. However, growing concerns about their adverse effects—such as tendon degeneration, delayed healing, and increased risk of surgical complications—have prompted a shift toward biologic alternatives. Our findings indicate that the combination of hyaluronic acid (HA) and platelet-rich plasma (PRP) provides the most promising clinical outcomes among currently available injectable treatments. The combination yielded significant improvements in patient-reported outcomes, including the Visual Analog Scale (VAS), Constant-Murley Score (CMS), and American Shoulder and Elbow Surgeons (ASES) score, particularly in the short term (0–12 weeks). These benefits align with previous findings in knee osteoarthritis, where HA+PRP also outperformed either substance alone, likely due to their synergistic effect on tissue regeneration and inflammation control [58-60].

Importantly, while the superiority of HA+PRP was evident in the early phase following injection, no significant differences were observed between the different treatment modalities at the six-month mark. This temporal pattern suggests that the therapeutic advantage of biologics may be most pronounced during the critical early window when pain reduction enables earlier participation in rehabilitation[61]. Accelerated engagement in physiotherapy has been consistently associated with better functional outcomes, particularly in partial tendon injuries. Nevertheless, further research is required to assess the long-term durability of these improvements and to clarify the potential role of repeated injections or adjunctive therapies[62, 63].

Parallel to conservative management, the second part of this work addressed an increasingly recognized problem in shoulder surgery: infections related to Cutibacterium acnes. This bacterium, part of the normal skin flora, resides deep within sebaceous glands and hair follicles, making it difficult to eradicate using standard alcohol- or chlorhexidine-based disinfectants. Postoperative infections caused by *C. acnes* are particularly problematic due to their indolent nature, often resulting in delayed diagnosis, chronic inflammation, and implant failure [2, 22, 36, 64, 65].

Our study confirms that 5% benzoyl peroxide (BPO) is significantly more effective than conventional antiseptics in reducing *C. acnes* colonization on the skin surface. BPO's lipophilic nature allows it to penetrate the deeper layers of the skin, reaching the pilosebaceous units where *C. acnes* proliferates. These findings are supported by previous studies showing that multiple applications of BPO—especially when started 48 to 72 hours before surgery—lead to significant reductions in bacterial load. Although some inconsistencies exist in the literature, particularly regarding BPO concentrations and application protocols, the overall trend supports BPO as a highly effective and well-tolerated preoperative antiseptic [5, 6].

The combination of BPO with clindamycin, widely used in dermatology for acne treatment, may offer added benefit by targeting microbial resistance and providing deeper dermal penetration. While our data did not reveal a statistically significant improvement over BPO alone, this approach merits further investigation, particularly in high-risk surgical populations. Other agents, such as hydrogen peroxide and miconazole nitrate, have also shown promise, though their clinical application in orthopedic settings remains limited at this stage [6, 35].

Taken together, the two thematic pillars of this dissertation—biologic therapy and infection prevention—highlight the potential of a more integrative and evidence-based approach to shoulder care. By reducing dependence on corticosteroids and enhancing infection control strategies, clinicians may be better equipped to improve both short- and long-term outcomes in patients undergoing conservative or surgical treatment.

Future research should focus on establishing standardized treatment protocols, including optimal timing, dosing, and combination regimens for HA+PRP and BPO-based antisepsis. Moreover, prospective multicenter trials and real-world data registries are essential to evaluate long-term effectiveness, cost-efficiency, and broader applicability across diverse patient populations. Integrating these findings into clinical practice may pave the way toward safer, more effective, and patient-centered shoulder care in both conservative and surgical contexts.

### 9.2.Strengths

One of the primary strengths of our research is the dual focus on two distinct but complementary challenges in shoulder care: improving pain management and function

through optimized conservative treatments and reducing postoperative infection risks through more effective skin antisepsis. This broader perspective enhances the practical relevance and potential clinical impact of the findings. From a methodological standpoint, both analyses were conducted with a high level of rigor. We performed systematic literature searches and network meta-analyses using clearly defined inclusion and exclusion criteria. In the case of PTRCT treatment, we strictly limited our sample to studies involving partial-thickness tears only, deliberately excluding those on tendinitis, tendinosis, or full-thickness tears. This ensured that our patient population was clinically homogeneous, increasing the internal validity of our results. Another notable strength is the use of up-to-date, high-quality randomized controlled trials (RCTs). Our comprehensive review included all eligible studies available in the literature, making this one of the most complete comparative assessments to date. Moreover, our findings are in line with international studies, enhancing the external validity and applicability of our results across various healthcare systems and populations. The clinical relevance of both topics cannot be overstated. Injection therapies are widely used in daily orthopedic practice, and *C. acnes*-related infections represent a persistent and costly challenge in shoulder surgery. Our findings provide evidence-based insights that directly support more informed and effective clinical decision-making.

### 9.3.Limitations

Despite its strengths, our study also has several limitations that should be considered when interpreting the results. First, in the injection therapy analysis, we encountered significant heterogeneity in the included studies. This includes variations in the specific substances used (e.g., different types of corticosteroids, HA formulations, or PRP preparation methods), dosing regimens, and injection techniques. Such variability makes direct comparison difficult and may influence outcome consistency. Second, most studies only reported short- to medium-term outcomes, typically up to six months. While this time frame is clinically relevant for assessing early pain relief and functional improvement, it limits our ability to evaluate the long-term effects or recurrence rates associated with each therapy. Similarly, in the antiseptic study, outcomes were limited to surface bacterial colonization without data on actual intraoperative contamination or infection rates, which would have provided a more definitive assessment of clinical effectiveness. Another challenge was the limited number of eligible high-quality RCTs,

particularly in the field of injection therapies. Our strict inclusion criteria, while necessary to maintain methodological rigor, resulted in the exclusion of a large number of potentially relevant studies. This reduces the overall sample size and may increase the risk of publication bias. Data reporting inconsistencies in some included studies also presented difficulties. In several cases, statistical details such as variance or standard deviations were missing or inaccurately reported, requiring us to contact study authors or make conservative assumptions during analysis. Furthermore, variations in PRP composition and HA concentration across studies introduced additional uncertainty.

Finally, although our analysis was comprehensive, further research is needed to confirm these findings in larger, more standardized, and longer-term studies.

## 10. CONCLUSIOS

Our research addressed two critical aspects of modern shoulder care: the optimization of conservative treatment for partial-thickness rotator cuff tears (PTRCTs) and the prevention of postoperative infections associated with Cutibacterium acnes in shoulder surgery.

Based on our network meta-analysis, we conclude that the combination of hyaluronic acid (HA) and platelet-rich plasma (PRP) is currently the most effective injectable therapy for PTRCTs, offering superior short-term outcomes in both pain relief and functional improvement compared to corticosteroids and monotherapies. These findings support the reconsideration of existing treatment guidelines to include HA+PRP as a preferred first-line option in conservative rotator cuff management.

In parallel, our analysis of preoperative skin antisepsis demonstrates that 5% benzoyl peroxide (BPO) is the most effective agent for reducing *C. acnes* colonization on the skin surface. Given the organism's role in implant-related shoulder infections and the limited efficacy of conventional antiseptics, our results support the inclusion of BPO in infection prevention protocols for shoulder surgery.

Together, these findings highlight the importance of integrating biologic therapies and evidence-based infection control measures into clinical practice to improve patient outcomes in both surgical and non-surgical settings.

## 11. IMPLEMENTATION FOR PRACTIC

In light of recent evidence, this proposal outlines recommended updates to clinical practice in the treatment of partial-thickness rotator cuff tears (PTRCTs) and in the preoperative preparation of patients undergoing shoulder surgery. The aim is to enhance patient outcomes through the integration of regenerative biologic therapies and more effective infection prevention strategies.

For the conservative management of PTRCTs, the combination of hyaluronic acid (HA) and platelet-rich plasma (PRP) has demonstrated superior short-term outcomes in terms of pain relief and functional improvement compared to corticosteroids or either biologic agent used alone. Based on these findings, we recommend that HA+PRP injections be adopted as a first-line therapy in appropriate patient populations. These include individuals at risk of corticosteroid-related complications, patients requiring rapid return to physical therapy, or those unresponsive to traditional steroid treatments.

HA and PRP may be administered simultaneously, using validated preparation techniques and standardized dosages. Administration should be followed by early initiation of physiotherapy, provided the patient's condition allows. Prior to treatment, patients must be informed of the biologic nature of the therapy, the expected benefits, and the current evidence supporting its efficacy. Informed consent should be obtained.

In parallel, shoulder surgery protocols should be revised to include preoperative decolonization using 5% benzoyl peroxide (BPO). This compound has proven more effective than standard alcohol- and chlorhexidine-based antiseptics in reducing Cutibacterium acnes colonization, which is a leading cause of infections in shoulder procedures. We recommend instructing patients to apply 5% BPO topically to the surgical area once daily for three consecutive days prior to surgery. This should be used in combination with standard intraoperative antiseptic measures. Patients should be screened for hypersensitivity to BPO and monitored for skin irritation.

To support the successful implementation of these updates, training sessions should be organized for clinical staff, including orthopedic surgeons, nurses, and physiotherapists. Instruction should cover HA+PRP preparation and administration, as well as patient education regarding BPO use. Additionally, outcome data—including post-injection recovery metrics and postoperative infection rates—should be collected and monitored

through a clinical registry. Regular audits are recommended to ensure adherence to the updated protocols and to facilitate evidence-based refinements over time[66, 67].

By integrating biologically active therapies and modern antiseptic strategies, this protocol has the potential to improve both non-operative and surgical outcomes in shoulder care, while aligning practice with the latest clinical research.

## 12. IMPLEMENTATION FOR RESEARCH

The findings of this study provide a valuable platform for the advancement of clinical and translational research in two key domains of shoulder care: the use of biologic injection therapies for partial-thickness rotator cuff tears (PTRCTs) and the optimization of preoperative antiseptic strategies to prevent Cutibacterium acnes-related infections in shoulder surgery.

One of the most important research implications lies in the need to explore the long-term effects of hyaluronic acid (HA) and platelet-rich plasma (PRP) combination therapy. Although this study demonstrated clear short-term benefits in terms of pain reduction and functional improvement, there is limited evidence regarding the durability of these outcomes. Future randomized controlled trials with extended follow-up periods (e.g., 12–24 months) are necessary to determine whether the observed benefits persist and to assess their influence on tendon structure, healing quality, and re-tear rates. Advanced imaging techniques, such as MRI and ultrasound, could be used to objectively evaluate tendon morphology and degeneration over time.

Moreover, the standardization of biologic therapies remains a pressing concern. Inconsistent preparation methods for PRP, variability in platelet concentrations, leukocyte content, and differing HA formulations hinder the comparability and reproducibility of studies. Future research should aim to define optimal preparation protocols and adopt universally accepted reporting standards to improve methodological consistency and facilitate meta-analyses. Mechanistic studies investigating the cellular and molecular effects of HA+PRP—such as their influence on tenocyte proliferation, extracellular matrix regeneration, and inflammatory modulation—could provide valuable insights into how these therapies support tissue repair.

In terms of infection prevention, the demonstrated effectiveness of 5% benzoyl peroxide (BPO) in reducing *C. acnes* colonization warrants further clinical investigation. While the current data support its use for superficial decolonization, future studies should assess its impact on deeper tissue colonization, intraoperative contamination, and actual surgical site infection rates. Randomized clinical trials comparing BPO to traditional antiseptics in shoulder surgeries—especially those involving prosthetic implants—are essential for validating its inclusion in standardized preoperative protocols. Further research could also

examine optimal application regimens, patient compliance, tolerability, and potential effects on the broader skin microbiome.

In addition, future studies may explore how these two strategies—biologic injections and advanced antisepsis—can be integrated into a single patient care pathway. For instance, patients receiving HA+PRP for conservative management may later require surgery, raising questions about the timing and interaction of these interventions. Research examining whether prior biologic injections influence surgical healing or infection risk would be highly relevant in clinical settings.

Finally, multicenter collaboration and real-world data collection will be key to successfully translating these findings into widespread clinical practice. Establishing prospective registries and harmonizing data collection protocols across institutions can help generate high-quality evidence, ensure external validity, and drive the development of future clinical guidelines. Through a combined effort of clinical trials, basic science, and implementation research, these findings have the potential to inform safer, more effective, and more personalized approaches to shoulder care.

## 13. IMPLEMENTATION FOR POLICYMAKERS

Let’s face it: steroids have had their time in the spotlight, but it's 2025, and we have better options. Our findings show that the combination of hyaluronic acid and platelet-rich plasma (HA+PRP) isn’t just science fiction—it actually works. It reduces pain, improves function, and doesn’t carry the long-term risks associated with corticosteroids. If policies still treat steroids as the gold standard, it’s time for an upgrade.

On the surgical side, Cutibacterium acnes continues to be the uninvited guest at every shoulder implant operation. Traditional skin disinfectants just are not cutting it. But here comes 5% benzoyl peroxide—the unexpected hero borrowed from teenage acne treatment—proving it’s not just for oily foreheads anymore. It significantly reduces bacterial load and could help prevent those pesky (and expensive) post-op infections.

In short: if we can update our phones every year, we can definitely update our clinical protocols. Back evidence-based policies, support access to biologic injections, and swap the old antiseptics for something that actually works. Shoulders across the country will be forever grateful.

## 14. FUTURE PERSPECTIVES

Evidence-based medicine is and remains to be the cornerstone of anesthesia and intensive care medicine. Scientific decision-making in these domains affects the prognosis of our patients. Furthermore, practitioners in these fields need to be accountable for their decisions. Our main aim was to approach protocols necessary to practice evidence-based medicine: in one study, we evaluated the validity of a protocolized intervention, and in the other study, we investigated the roadmap to protocolizing an intervention by contextualizing and summarizing currently available literature. I intend to continue the work of practicing and popularizing evidence-based medicine for the entire duration of my medical career.

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## 16.1. Publications related to the thesis


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## 16.2. Publications not related to the thesis


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Meta-analysis

# Hyaluronate Acid Plus Platelet-Rich Plasma Is Superior to Steroids for Pain Relief Less Than 6 Months Using Injection Therapy of Partial Rotator Cuff Tears: A Systematic Review and Network Meta-analysis

Viktor Weninger, M.D., Gergely Agócs, Ph.D., Norbert Kovács, M.D., Szilárd Váncsa, M.D., Luca Hergár, M.D., Chan Ju Baek, Péter Hegyi, M.D., DSc., Gergely Holnapy, Ph.D., and Gábor Skaliczki, M.D., Ph.D.

**Purpose:** To compare the efficacy of steroid injections to other injectable therapies in partial-thickness rotator cuff (RC) tears. **Methods:** A systematic literature search was performed until October 25, 2021, in 3 databases (Cochrane Central Register of Controlled Trials, Embase, MEDLINE). Eligible studies compared the efficacy of steroid, hyaluronic acid (HA), platelet-rich plasma (PRP), the combination of HA and PRP (HA + PRP), and adipose-derived regenerative cells in RC tears. The primary outcomes were the visual analog scale (VAS), Constant-Murley Shoulder Outcome Score (CMS) and American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form. Using paired and network meta-analysis, we calculated pooled mean differences (MDs) with 95% confidence intervals (CIs). **Results:** We included a total of 7 articles in the quantitative synthesis. In shorter periods, the HA + PRP combination was superior to the other substances we investigated (HA + PRP: VAS [0-4 weeks]: MD: −0.99 [95% CI, −1.62 to −0.36]; CMS [0-3 months]: 20.56 [95% CI, 16.18 to 24.94]. This combination was followed by the use of HA or PRP alone, depending on the duration of follow-up and the outcome being studied. In our study, short-term results suggest that saline is superior to steroids for partial tears, but this trend is reversed at 6-month follow-up. **Conclusions:** The HA and PRP combination is currently the most effective in partial RC tear treatment in the short term. After 6 months, there is no meaningful difference, so the benefits of the combination are short term. **Level of Evidence:** Level II, systematic review and meta-analysis of Level I and II studies.

*See commentary on page 316*

Rotator cuff (RC) tears are associated with pain and activity limitation.[1] RC disorders increase with age, reaching up to 60% of the population over 80.[2,3] RC tears can be divided into full-thickness tears and partial-thickness rotator cuff tears (PTRCTs).[4,5] Cadaveric and magnetic resonance imaging (MRI) studies have reported the incidence of PTRCTs to range from 13% to 30%, with increasing incidence with age.[6-9]

Initial treatment of PTRCTs is often nonsurgical, consisting of physiotherapy,[10,11] analgesics, nonsteroidal anti-inflammatory drugs, or various injectable agents, such as steroids, platelet-rich plasma (PRP), hyaluronic acid (HA), or adipose-derived regenerative cells (ADRCs).[12-14] Despite their widespread use, there is no clear evidence in the literature as to which type of injection carries the greatest benefit.[1] Steroid injections

*From the Department of Orthopedic Surgery, Semmelweis University, Budapest, Hungary (V.W., L.H., C.J.B., G.H., G.S.); Centre for Translational Medicine, Semmelweis University, Budapest, Hungary (V.W., G.A., N.K., S.V., L.H., P.H., G.H., G.S.); Department of Biophysics and Radiation Biology, Semmelweis University, Budapest, Hungary (G.A.); Doctoral School of Clinical Medicine, University of Szeged, Szeged, Hungary (N.K., S.V.); Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary (N.K., S.V., P.H.); and Institute of Pancreatic Diseases, Semmelweis University, Budapest, Hungary (P.H.).*

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*Address correspondence to Gábor Skaliczki, M.D., Ph.D., Department of Orthopedic Surgery, Semmelweis University, 1085 Budapest, Üllői út 26, Hungary. E-mail: skaliczki@gmail.com*



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are commonly used and considered the gold standard treatment. Although they provide excellent short-term pain relief, they are not harmless, and their use may not modify the course of the disease. In addition, steroid injections can induce nontenocyte differentiation in the human tendon, which promotes degenerative processes and potentially leads to rupture; their long-term use may also induce arthropathic changes.[15] Moreover, several studies have reported that preoperative corticosteroid injections might be associated with an increased risk of revision surgery following RC surgery in a time- and dose-dependent manner.[16-18]

Numerous recently published articles assessed the efficacy of other injection agents, such as HA, PRP, ADRCs, and their combinations.[19-29] Results have shown a beneficial effect of these novel injection therapies compared with using steroids.

The purpose of this study was to compare the efficacy of the steroid injections to other injectable therapies in PTRCTs. We hypothesize that there is a better injection therapy than the steroid injection currently used in our practice for treating PTRCTs.

## Methods

We have reported this network meta-analysis and systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[30] Our protocol was registered on PROSPERO under the registration number CRD4202 1285416. Contrary to our protocol, we did not find studies comparing collagen and nonsteroidal anti-inflammatory drugs. Furthermore, we did not have enough data to investigate the Western Ontario Rotator Cuff Index, range of motion, side effects, infections, and complications.

### Search Strategy

A systematic search was conducted in MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials, for studies published up until October 25, 2021. The following search terms were used in all databases: (injection OR steroid OR methylprednisolone OR betamethasone OR triamcinolone OR lidocaine OR NSAID OR saline OR 'sodium chloride' OR corticosteroid OR conservative OR PRP OR 'platelet rich plasma' OR 'stem cell' OR collagen OR hyalur* OR prolotherapy). No restrictions were applied during the search. In addition, the reference lists of the included studies were screened for additional eligible articles.

### Eligibility Criteria and Selection Strategy

The yield of the search was combined with reference manager software (EndNote X9; Clarivate Analytics). After the automatic and manual removal of duplicate records, 2 independent authors (L.H., V.W.) evaluated the titles, abstracts, and full texts of all studies. First, we performed a primary selection based on title and abstract simultaneously. Then, we assessed full texts for inclusion. Finally, a third author (G.S.) resolved disagreements.

We used the PICO framework to assess study eligibility. We included only randomized controlled trials (RCTs) that investigated patients having PTRCT (P) and that compared different injection therapies (I: HA, PRP, ADRCs, saline injections; C: steroid injection). The outcomes (O) we examined were clinical scores on the visual analog scale (VAS),[31] Constant-Murley Shoulder Outcome Score (CMS),[32] and American Shoulder and Elbow Surgeons (ASES) Standardized Shoulder Assessment Form.[33] We examined the change in these clinical scores from baseline (immediately before injection) to different post-treatment intervals.

Partial tears were confirmed by magnetic resonance imaging (MRI) scans. Studies were included if the partial RC tear was isolated, was not a full-thickness tear, and was not associated with other pathology. Abstracts and gray literature (preprints and other non–peer-reviewed material) were excluded from the analysis.

### Data Extraction

Two independent review authors (L.H. and V.W.) extracted data in duplicate into a standardized data collection form (Microsoft Excel 365; Microsoft Corporation). Disagreements were resolved by a third party (G.S.). We used a standardized data collection sheet to collect all the necessary data: first author; publication year; study design; clinical outcome (dependent variable), measured using the VAS for pain assessment ranging from 0 (best, i.e., no pain) to 10 (worst, i.e., extreme pain); the ASES, ranging from 0 (worst) to 100 (best) (it consists of 2 dimensions: pain and activities of daily living); the CMS with both subjective and objective components, ranging from 0 (worst) to 100 (best); and the means, standard deviations, medians, ranges, and interquartile ranges related to clinical scores. A third party (G.S.) resolved discrepancies.

### Data Analysis

In assessing transitivity, we qualitatively evaluated epidemiologic effect modifiers, with a particular focus on age and the specific study populations as primary factors. This involved systematically comparing these effect modifiers across all intervention groups to ensure comparability of the included studies. Table 1 summarizes the main effect modifiers accompanying this analysis to provide a clear overview of their impact on the network meta-analysis outcomes.[34]

We included the following outcomes in the final analysis: CMS (baseline to 3 months and baseline to 6 [in 1 case 7] months), VAS (baseline to 4 weeks and baseline to 6 months), and ASES (baseline to 6 months). The effect size was the mean difference (MD)

**Table 1.** Main Characteristics of the Included Studies

| Author (Year) | Study Type | Study Period | Total Number of Patients | Population Inclusion Criteria (Verbatim) | Population Exclusion Criteria (Verbatim) | Interventions | Number of Patients in Each Group | Outcomes |
|---|---|---|---|---|---|---|---|---|
| Chou et al., 2010, Taiwan[19] | Prospective, randomized trial Level I | NA | 51 patients (median age NA, 32) | Patients who had pain around the shoulder, a positive impingement sign, rotator cuff pathology without a complete tear; not responding to conservative therapy for at least 3 months; between 35 and 80 years | Rheumatic diseases, glenohumeral osteoarthritis, full-thickness cuff tears, fractures, infections, or tumors; hypersensitivity to hyaluronate; participated in any other study within 3 months; had received a subacromial injection within 3 weeks; pregnant or wanted to become pregnant | HA vs saline<br>HA: ARTZ Dispo, 25 mg SH<br>Placebo: 0.9% normal saline solution, at 2.5 mL/syringe, in the same package | 25 vs 26 | Constant score, VAS score, global tolerability assessed by the physician weeks 1, 2, 3, 4, 5, 6, 12 |
| Moghtaderi et al., 2013, Iran[20] | Prospective, randomized trial Level I | NA | 40 (NA, NA) | Between 30 and 80 years, a positive Neer and Hawkins sign, and a positive ultrasonographic diagnosis without a complete tear, did not respond to conservative treatments at least 6 months | Rheumatic disease, glenohumeral osteoarthritis, full-thickness tears, fractures, diabetes mellitus, infections, or tumors; had hypersensitivity to hyaluronate; had participated in any other study within 6 months; subacromial injection within 8 weeks; pregnant; were at risk of complications of intra-articular injections such as patients who had received anticoagulant | HA vs saline<br>Fermathron, 20 mg/2 mL sodium hyaluronate The placebo was 0.9% normal saline solution, at 2 mL/syringe. Both groups received 3 weekly injections in a same protocol. | 20 vs 20 | Constant score, VAS score 1, 2, 3, 12 weeks after treatment |
| Shams et al., 2016, Egypt[22] | Prospective, randomized trial Level II | 2013-2015 | 40 patients (mean age 51 ± 11 years, 19fm) | MRI evidence of a partial supraspinatus tear | Generalized inflammatory arthritis, infection, osteoarthritis of the shoulder, nerve-related symptoms, known malignancy, and bleeding disorders | PRP vs steroid<br>PRP: aspirated with citrate dextrose anticoagulant; it was centrifuged at 3,500 rpm for 10 minutes. Upper 4 mL, which represents the platelet-poor plasma phase, was discarded. The remaining above the gel was the PRP phase. Corticosteroid injection: | 20 vs 20 | 6 and 12 weeks, 6 months: ASES, CMS, SST, VAS 6 months after the intervention MRI grade |

(continued)

**Table 1.** Continued

| Author (Year) | Study Type | Study Period | Total Number of Patients | Population Inclusion Criteria (Verbatim) | Population Exclusion Criteria (Verbatim) | Interventions | Number of Patients in Each Group | Outcomes |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Kenacort-A 40 mg, (triamcinolone) | | |
| Cai et al., 2019, China[23] | Prospective, randomized trial Level I | 2014-2016 | 184 patients (mean age NA, 85) | PTRCT diagnosed by clinical examination and MRI | Elderly patient >60 years, RC tears secondary to fracture, prior operation, prior other drug intervention, pregnant, shoulder pain induced by non-RC tear, active infection, hemoglobin <7.0 g/dL or platelets <15,000/nL | Saline vs HA vs PRP vs HA + PRP<br>Saline: 4 mL saline<br>Hyaluronate: 4 mL HA<br>PRP: (20 mL) collected from each patient was injected into an anticoagulant tube centrifuged at 4°C for 10 minutes at 1,500 rpm; SH + PRP group was treated with 2 mL PRP and 2 mL SH. | 47 vs 44 vs 45 vs 48 | Constant score, ASES, and VAS scores, 1, 3, 6, 12 months |
| Schwitzguebel et al., 2020, Switzerland[25] | Prospective, randomized trial Level I | 2015-2016 | 80 adults, NA, 35fm | Interstitial supraspinatus tear | Concomitant tendon tears; a frozen shoulder, defined as a restriction of 20% in external rotation as well as active and passive elevation, shoulder steroid infiltrations past 3 months; calcifying tendinopathies | PRP vs. saline<br>PRP: centrifugation for 5 minutes at 1,500 rpm, collection of 2 mL of the platelet-rich supernatant<br>Saline: saline solution | 41 vs 39 | 7 months after the intervention: lesion volume, calculated on MRA, VAS, SANE, CMS, ASES, adverse events, additional treatments after 7- and 12-month follow-up with VAS and SANE |
| Hurd et al., 2020, U.S.A.[27] | Prospective, randomized trial Level II | 2016-2017 | 16 patients (mean age NA, 3) | Radiologists and the treating orthopaedic shoulder specialist; had to correlate with findings from clinical examination to come to the diagnosis of PTRCT | Full-thickness tear, insufficient amount of subcutaneous tissue, malignancy, immunosuppressant therapy; received a corticosteroid injection in last 3 months; severe arthrosis, fatty atrophy, previous surgeries, tobacco use, liver disease or an alanine aminotransferase value >400, allergy to sodium citrate, pregnancy | UA-ADRCs vs steroid<br>UA-ADRCs: $11.4 \times 10^6$ UA-ADRCs in 5 mL liquid<br>Corticosteroid: 80 mg methylprednisolone plus 3 mL 0.25% bupivacaine | 11 vs 5 | ASES score, RAND score, VAS score, size of the PTRCT compared to baseline<br>Weeks 3, 6, 9, 12, 24, 32, 40, and 52 post-treatment; MRI scans were performed at BL and weeks 24 and 52 post-treatment. |
| Thepsoparn et al., 2021, Thailand[29] | Prospective, randomized trial Level II | 2019-2020 | 31 patients (mean age NA, 25) | 18 and 80 years and no serious systemic diseases, partial supraspinatus | Severe arthritis or other complications related to supraspinatus tears, | PRP vs steroid<br>PRP: centrifuged at 1500 rpm for 5 minutes | 15 vs 16 | 1- and 6-month VAS, OSS score |

(continued)

**Table 1.** Continued

| Author (Year) | Study Type | Study Period | Total Number of Patients | Population Inclusion Criteria (Verbatim) | Population Exclusion Criteria (Verbatim) | Interventions | Number of Patients in Each Group | Outcomes |
|---|---|---|---|---|---|---|---|---|
| | | | | tendon tears, natural history of tears from repetitive trauma or overuse only. Failed physical therapy and oral medication for at least 3 months. Ability to participate for a minimum follow-up period of 6 months. | previous shoulder surgery. Other concurrent shoulder conditions such as impingement. Malignancy. Current treatment using anticoagulant or antiplatelet medication. Immunocompromised status | Corticosteroid group: 1 mL triamcinolone acetonide (40 mg/mL Kenacort-A with 4 mL of 1% lidocaine) | | |

ASES, American Shoulder and Elbow Surgeons; BL, baseline; CMS, Constant-Murley Shoulder Outcome Score; fm, female; HA, hyaluronic acid; MRA, magnetic resonance arthrogram; MRI, magnetic resonance imaging; NA, not available; OSS, Oxford Shoulder Score; PRP, platelet-rich plasma; PTRCT, partial-thickness rotator cuff tear; RAND, RAND 36-Item Short Form Survey; RC, rotator cuff; rpm, revolutions per minute; SH, sodium hyaluronate; SANE, Single Assessment Numeric Evaluation; SST, simple shoulder test; UA-ASRC, uncultured, unmodified, autologous adipose-derived regenerative cell; VAS, visual analog scale.

in all cases. The mean and standard deviation of change to baseline values were extracted for each treatment arm directly or indirectly. We used the frequentist random effects network meta-analysis (NMA) method to compare interventions, assuming common between-study variance (tau squared) for every comparison.[35] The random-effects approach was used because of the inherent heterogeneity across studies, acknowledging that the true effect size may vary between different populations or settings. Multiarm study correlation was taken into consideration. The point and interval estimate for each intervention compared with a reference intervention (here: saline) was summarized in forest plots.[36] Treatment effect estimates for all comparisons were summarized in league tables.[30] The reliability of effect size estimates was evaluated by direct evidence plots.[37] Treatments were ranked by the *P*

-score ranking metric, calculated from the point estimates and standard errors, based on the principles of frequentist network meta-analysis under the assumption of data normality. These scores provide a statistical measure of the average confidence that 1 treatment is superior to its competitors across all comparisons within the network.[38] A higher score represents a higher confidence in the given intervention. We used the meta,[36] netmeta,[39] and dmetar[40] packages of R.[41] The confidence interval (CI) ($1 - \alpha$) was set to 95%.

In each figure, we included the following: the network plot illustrates the number of direct comparisons available with the number of studies and the total number of patients for each comparison, the forest plot shows the effect sizes compared with saline, and the rank-order plot illustrates the *P* scores.

### Risk of Bias Assessment

The risk of bias assessment was performed independently by 2 authors (V.W. and C.J.B.) using the RoB 2 tool for randomized controlled trials recommended by the Cochrane Handbook.[19] Disagreements were resolved by consensus. We used the robvis app tool to visualize the risk of bias assessment.[42]

### Certainty of Evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group modality approach to assess the certainty of evidence.[43] The certainty of evidence was evaluated independently by 2 authors (V.W. and C.J.B.), and disagreements were resolved by consensus.

## Results

### Results of Search and Selection

A total of 7,512 records were identified through electronic database searches, of which 7 publications

were included.[7] The detailed selection process is described in the PRISMA flow diagram (Fig 1).

### Characteristics of the Included Studies

In Table 1, we summarize the main study characteristics. All included studies were single-center RCTs.[19,20,22,23,25,27,29] Of the 7 studies, 2 compared HA with saline as a placebo. One study compared HA with saline, PRP, and a combination of HA with PRP. Two different studies compared PRP with steroid therapy, 1 study compared PRP with saline, and 1 study compared uncultured, unmodified, autologous ADRCs with steroid therapy. Table 1 shows the main effect modifiers for assessing transitivity.

## Outcomes

### Change in Pain Using the VAS (0-4 Weeks)

Three studies with 266 participants and 5 intervention categories contributed to the NMA assessing VAS at 0 to 4 weeks (Fig 2).[19,23,29] The combination of HA and PRP (HA + PRP MD = −0.99 [95% CI, −1.62 to −0.36]; HA MD = −0.43 [95% CI, −1.01 to 0.14]; PRP MD = −0.17 [95% CI, −0.73 to 0.40]; and steroid MD = 0.43 [95% CI, −1.50 to 2.36]) was the most effective in decreasing the VAS score in the first 4 weeks compared with saline. Interestingly, the steroid seemed to be the least effective. However, the difference was nonsignificant compared with saline. HA + PRP had the highest likelihood of achieving a decrease in VAS score, considering both direct and indirect comparison. Based on the rank plot, HA + PRP ($P$ = .966) proved to be the most effective treatment, followed by HA ($P$ = .648) and PRP (P = .416) alone, then saline ($P$ = .254) and steroid ($P$ = .216) as the least effective agent.

### Change in Pain Using the VAS (0-6 Months)

Four studies with 312 participants and 6 intervention categories contributed to the NMA assessing VAS after 6 months (Fig 3).[23,25,27,29] The combination of HA and PRP (HA + PRP MD = −3.00 [95% CI, −6.09 to 0.08]; HA MD = −1.59 [95% CI, −4.69 to 1.51]; PRP MD = −1.59 [95% CI, −3.97 to 0.79], ADRC MD = −0.88 [95% CI, −7.07 to 5.31]; and steroid MD = 0.91 [95% CI, −3.45 to 5.26]) was the most effective in decreasing VAS scores 6 months after the intervention compared with saline, but our results are

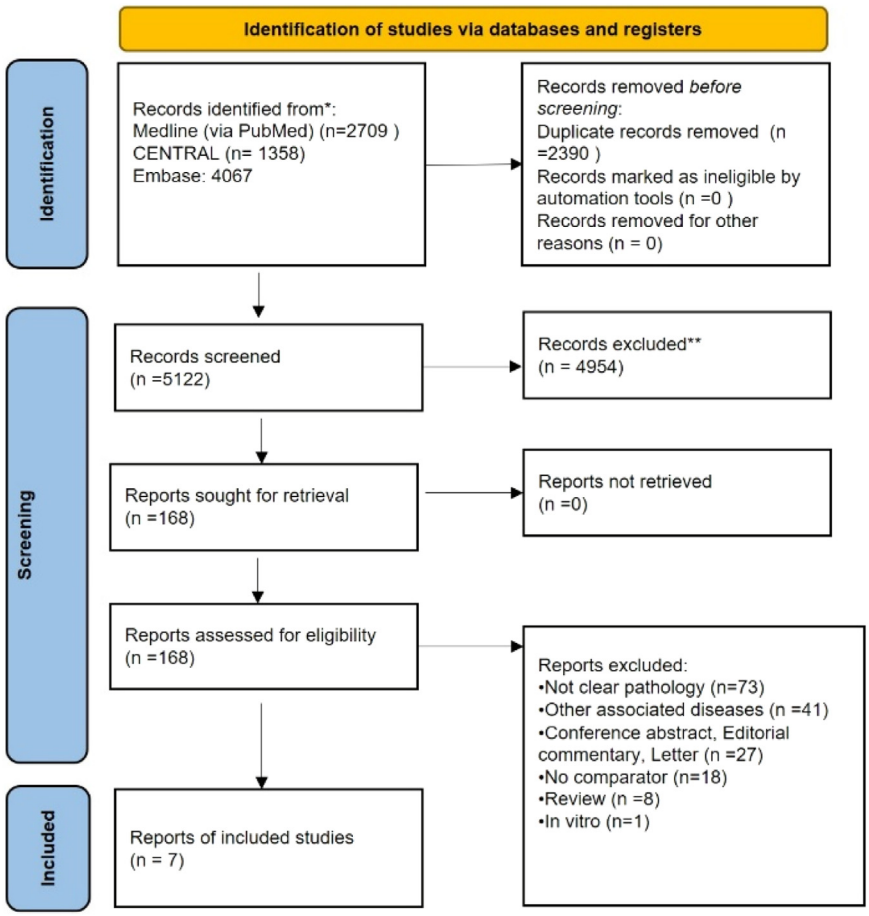


**Fig 1.** Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram.

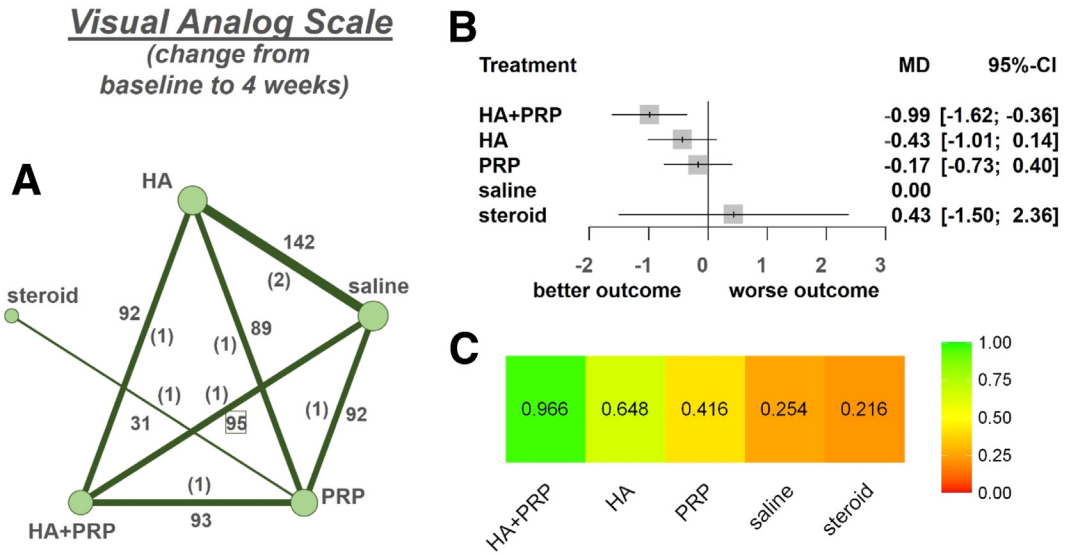


**Fig 2.** Summary figure for the change between baseline and 4 weeks in pain measured using the visual analog scale. (CI, confidence interval; HA, hyaluronic acid; MD, mean difference; PRP, platelet-rich plasma.)

statistically not significant. Based on the rank plot, the most effective treatment was HA + PRP ($P$ = .854), followed by HA ($P$ = .619), PRP ($P$ = .595) and ADRC ($P$ = .496), then saline ($P$ = .266) and steroid (i = .170) as the least effective method.

### Change in the CMS (0-3 Months)

Four studies with 315 participants and 5 intervention categories contributed to the NMA assessing CMS from 0 to 3 months (Fig 4).[19,20,22,23] The combination of HA and PRP (HA + PRP MD = 20.56 [95% CI, 16.18 to 24.94]; HA MD = 14.95 [95% CI, 11.05 to 18.86]; PRP MD = 11.82 [95% CI, 7.40 to 16.24]; steroid MD = −5.38 [95% CI, −18.10 to 7.34]) provided the best results in increasing the CMS in the first 3 months compared with saline. Based on the rank plot, the best treatment was HA + PRP ($P$ = .99).

### Change in the CMS (0-6 Months)

Three studies with 305 participants and 5 intervention categories contributed to the NMA assessing CMS at 0 to 6 months (Fig 5).[22,23,25] The combination of HA and PRP (HA + PRP MD = 23.40 [95% CI, −3.00 to 49.79]; PRP MD = 8.50 [95% CI, −11.71 to 28.71]; HA MD = 6.74 [95% CI, −19.67 to 33.15]; and steroid MD = 1.60 [95% CI, −35.41 to 38.60]) showed the most promising

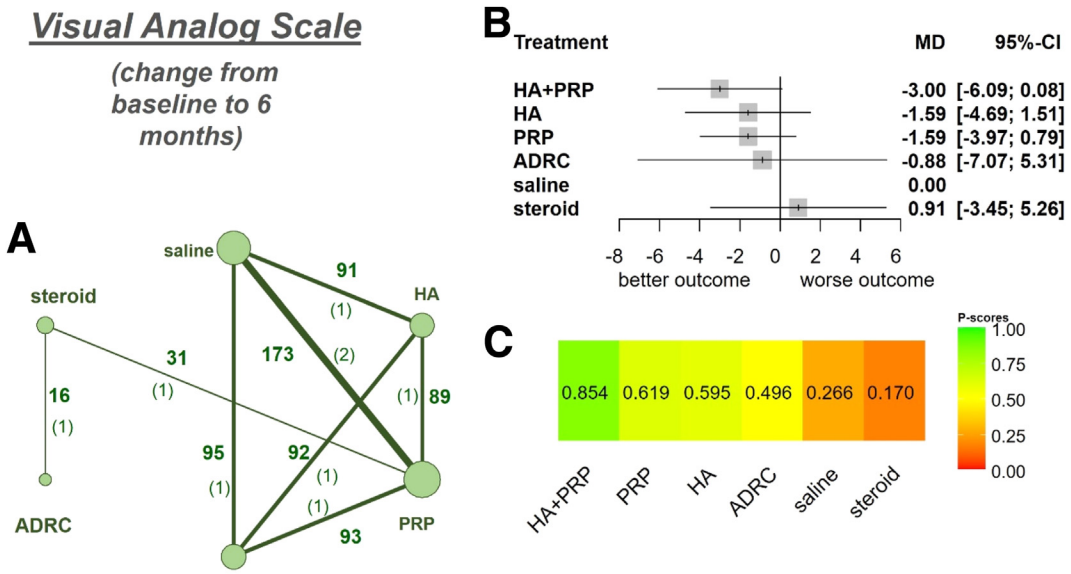


**Fig 3.** Summary figure for the change between baseline and 6 months in pain measured using the visual analog scale. (ADRC, adipose-derived regenerative cell; CI, confidence interval; HA, hyaluronic acid; MD, mean difference; PRP, platelet-rich plasma.)

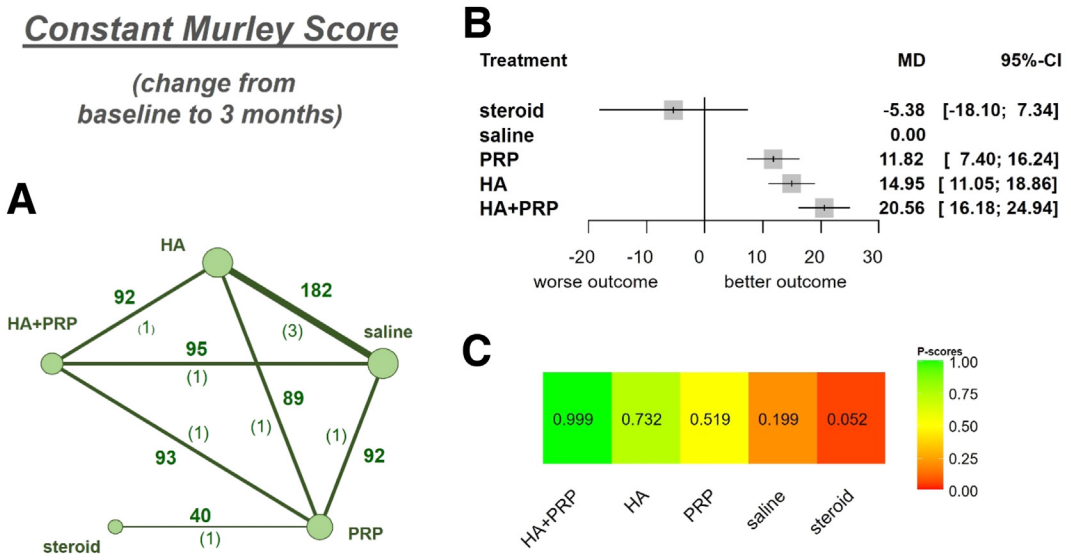


**Fig 4.** Summary figure for Constant-Murley Shoulder Outcome Score changes from baseline to 3 months. (CI, confidence interval; HA, hyaluronic acid; MD, mean difference; PRP, platelet-rich plasma.)

results in increasing the CMS in the first 6 months compared with saline. Saline was the least effective. The differences between saline and the other interventions were not significant. Based on the rank plot, the most effective treatment was HA + PRP ($P = .889$).

### Change in the ASES Score (0-6 Months)

Three studies with 305 participants and 5 intervention categories contributed to the NMA assessing ASES score at 0 to 6 months (Fig 6).[22,23,25] The combination of HA and PRP (HA + PRP MD = 28.02 [95% CI, −0.50 to 56.55]; PRP MD = 9.44 [95% CI, −12.64 to 31.51]; HA MD = 6.80 [95% CI, −21.77 to 35.37]; and steroid MD = 5.04 [95% CI, −33.48 to 43.55]) appeared to be the most effective injection therapies in increasing the ASES score half a year after the initial intervention. Saline and steroid injection were the least effective. Based on the rank plot, the most effective treatment was HA + PRP ($P = .910$).

### Risk of Bias Assessment

Most of the included articles were judged as "low" to moderate ("some concerns") risk of bias, except 1 article, which had a high risk of bias (due to "bias in measurement in outcome").[29] A summary of the risk of bias assessment can be found in the appendix material (Appendix Figs 1-10, available at www.arthroscopyjournal.org).

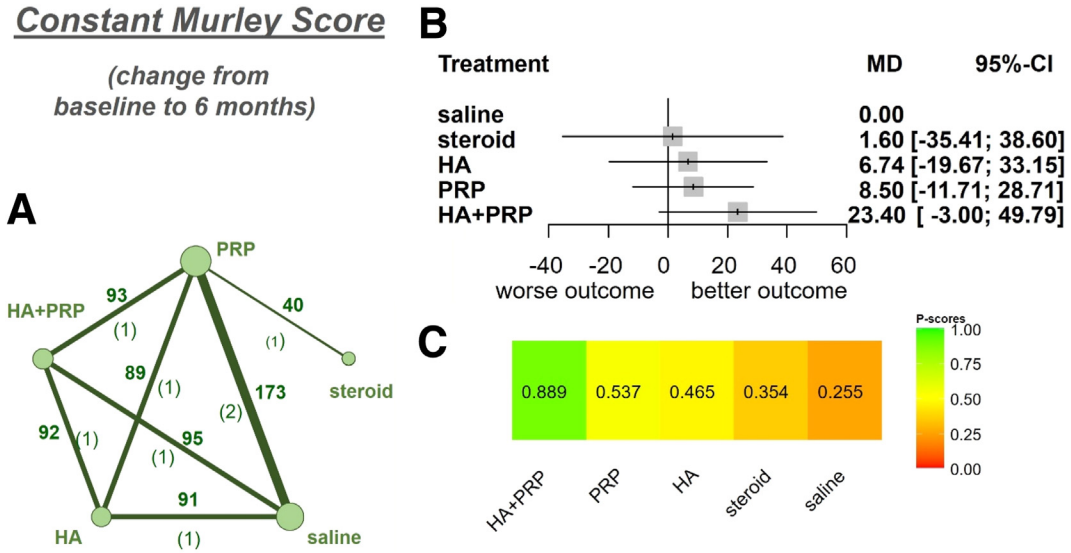


**Fig 5.** Summary figure for Constant-Murley Shoulder Outcome Score changes from baseline to 6 months. (CI, confidence interval; HA, hyaluronic acid; MD, mean difference; PRP, platelet-rich plasma.)

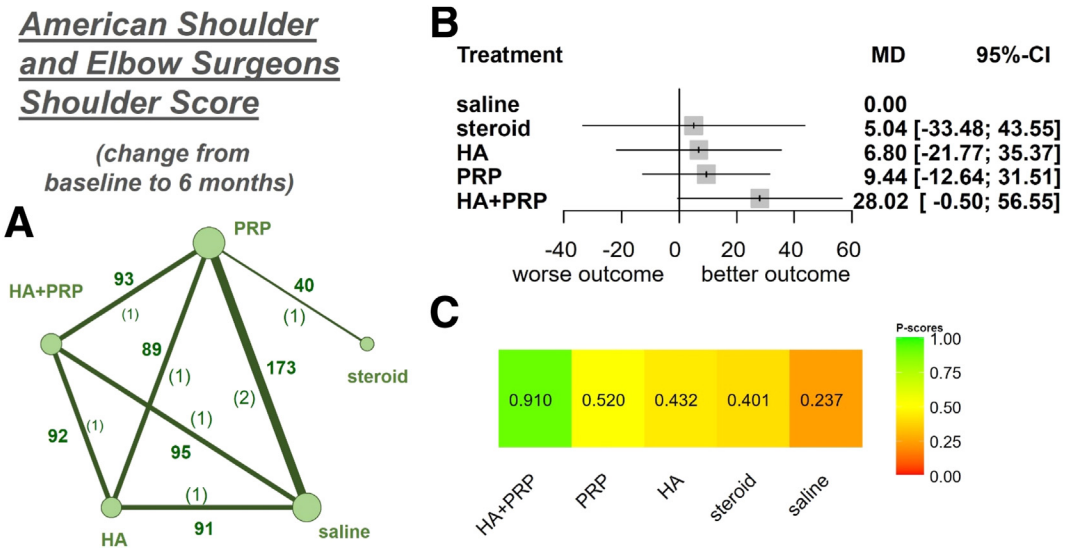


**Fig 6.** Summary figure for American Shoulder and Elbow Surgeons score changes from baseline to 6 months. (CI, confidence interval; HA, hyaluronic acid; MD, mean difference; PRP, platelet-rich plasma.)

### Certainty of Evidence

The quality of evidence in the studies was variable (Appendix Tables 2-6, available at www.arthroscopyjournal.org). The grade of evidence was of moderate or very low quality for each pairwise comparison between interventions.

Although we found some heterogeneity among the interventions and protocols, the basic therapeutic components of the interventions were maintained across studies, allowing a reasonable assumption of transitivity for this analysis.

## Discussion

Our study showed that the most effective injection therapy of PTRCT was HA plus PRP in terms of improvement in pain, CMS, and ASES. The combination of HA and PRP significantly improved VAS after 4 weeks and in CMS after 3 months compared with saline and showed better results than steroids. These results were followed by HA alone, followed last by the steroid.

The present NMA was conducted to compare different injection treatment modalities for PTRCT and to find the most effective among them. In the short term (0-4 weeks), the improvement of VAS was significant when using the HA + PRP combination compared with a placebo. However, there were no differences after 6 months. The same results were found for CMS, showing significantly better outcomes after 3 months and no significant differences after 6 months. The ASES score was examined only 6 months from the baseline, and again, the HA + PRP treatment dominated despite the nonsignificant results. We found that HA + PRP can improve shoulder function, as shown by CMS and ASES scores, and alleviate pain, as shown by VAS score. Based on our NMA, HA + PRP outperformed steroids in all the examined variables.

This combination not only is known in partial RC tears of the shoulder but has also been studied in osteoarthritis (OA) of various joints. A meta-analysis by Zhao et al.[44] and Karasavvidis et al.[45] showed that OA in the knee was treated more effectively with this combination than HA or PRP alone. A study by Satin et al.[46] demonstrated a positive in vitro effect of the PRP + HA combination on stimulating cell growth, restoring components of the joint extracellular matrix, and reducing inflammation. Cai et al.[23] suggested that HA and PRP can be administered simultaneously. When the 2 substances are administered simultaneously, the agent-specific beneficial effects are combined with the injected agent.

On the basis of our results, we observe that there are no significant differences between the different treatment regimens after 6 months. This may be because these agents are absorbed from the subacromial area over several months and thus their effect is also lost.[47,48] However, in the case of partial RC tears, the desired short-term effect of injection therapies is rapid pain and inflammation relief. The investigated injections begin to provide their anti-inflammatory and analgesic effects within days of their administration, so their short-term effects are clearly felt. The patient's complaints are relieved and the pain is reduced, so the patient can begin physiotherapy much earlier, which is crucial for rehabilitation.

### Implications for Research

Further RCTs are needed to obtain more precise results, excluding tendinitis, tendinosis, and full tear, with well-defined interventions, doses, and substances. We

have not found any article reporting data with a longer (1 or more years) follow-up; thus, studies including longer periods might be necessary. We were faced with inaccurate data reporting in some of our included publications, so we highly recommend following a rigorous data reporting system.

### Implications for Practice

On the basis of our results, we suggest a reconsideration of the use of steroids as the standard injection therapy for the conservative treatment of PTRCTs. The introduction of novel substances, such as the combination of HA + PRP, may be considered.

### Limitations

Our review has some limitations. The small number of articles increases the chance of bias. Due to our strict inclusion/exclusion criteria, many studies were dropped to avoid heterogeneity. The data reporting in some articles was inaccurate (e.g., variance was reported inaccurately), which we tried to balance by asking the authors for the raw data. It also complicated our investigation that publications used different active substances in the same group. For instance, 2 different types of steroids had been used—triamcinolone and methylprednisolone—which may have influenced our findings. It may also be problematic that the different studies used different PRP production methods and that the amount of PRP varied between studies. Similarly, the type and doses of HA used were also different. Due to bad data reporting in some of the included articles, we could only use conservative estimates. Patient-reported outcomes could not be included in our study. These cutoffs help to understand specific patient outcomes and allow clinicians to personally assess patient improvement, but our included articles did not include these data.[49] It is also important to emphasize that our maximum follow-up was 6 months. Therefore, conclusions can only be drawn within this time frame. Lastly, we examined transitivity, but due to the small number of articles, we could only assess qualitative transitivity, which we could not quantify.

## Conclusions

The HA and PRP combination is currently the most effective in partial RC tear treatment in the short term. After 6 months, there is no meaningful difference, so the benefits of the combination are short term.

## Disclosures

The authors report no conflicts of interest in the authorship and publication of this article. Full ICMJE author disclosure forms are available for this article online, as supplementary material.

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SHOULDER & ELBOW

# 5% benzoyl peroxide is the most efficient in reducing the cutibacterium flora of the shoulder skin: a network meta-analysis

Viktor Weninger[1,2], Gergely Agócs[2,3], Luca Hergár[1,2], Szilárd Váncsa[2,4,5], Bence Hegedűs[1,2], Imre Szerb[6,7], Péter Hegyi[2,4,5] and Gábor Skaliczki[1,2]

[1]Department of Orthopedic Surgery, Semmelweis University, Budapest, Hungary
[2]Centre for Translational Medicine, Semmelweis University, Budapest, Hungary
[3]Department of Biophysics and Radiation Biology, Semmelweis University, Budapest, Hungary
[4]Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary
[5]Institute of Pancreatic Diseases, Semmelweis University, Budapest, Hungary
[6]Uzsoki Street Hospital, Budapest, Hungary
[7]Department of Traumatology, Semmelweis University, Budapest, Hungary

Correspondence should be addressed to G Skaliczki: skaliczki@gmail.com

- *Purpose:* Our study aims to compare different perioperative treatments to reduce *C. acnes*, the most common causative agent of surgical site infections following shoulder surgery.
- *Methods:* A systematic search was performed in MEDLINE (PubMed), Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and the Web of Science for studies published up to October 20, 2022. We included randomized-controlled trails investigating the efficacy of different dermal preparation in reducing the *C. acnes* colonising the skin surface. The studies examined positive bacterial cultures before and after skin treatment. The included trials were able to compare seven different skin treatment methods. We performed a frequentist network meta-analysis and calculated pooled risk ratios (RRs) with 95% confidence interval (CI).
- *Results:* Our study could include comparisons of 946 different patients. The use of 5% benzoyl peroxide (BPO) and its combination with the antibiotic clindamycin was found to be the most effective in reducing *C. acnes* colonization on the skin (BPO 5% RR = 0.25, CI: 0.08–0.72, BPO with clindamycin RR = 0.25, CI: 0.04–1.50). Based on the rank plot, 5% BPO (P score: 0.808) was the most effective treatment, followed by BPO 5% with clindamycin (P score: 0.749). We could not perform a network meta-analysis regarding the efficacy of different dermal preparation in reducing *C. acnes* colonization on the dermis and in the joint.
- *Conclusion:* Cutibacterium colonization of the skin flora can be effectively reduced on the skin surface by the use of 5% BPO.

Keywords: propionibacterium; benzoil; hydrogen peroxide; peroxide; infection; infection control; Cutibacterium; *C. acnes*

## Introduction

Shoulder surgery is a frequently performed orthopaedic procedure (1, 2). Infection after shoulder surgery is one of the most serious complications for the patient. Patients with postoperative wound infection are more likely to spend time in intensive care and have higher morbidity rates than patients without postoperative infection (3, 4). Several attempts have been made to provide reliable, consistent, reproducible methods to decolonize or

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eradicate pathogens preoperatively to reduce the risk of surgical site contamination and infection (5).

*Cutibacterium acnes* (*C. acnes*), formerly *Propionibacterium acnes*, is a Gram-positive, facultatively anaerobic bacterium in the normal skin microbiome. It colonizes primarily the sebaceous glands and hair follicles of human skin and is usually non-pathogenic. However, it can also be an opportunistic pathogen, causing invasive and implant-related infections as the bacterium proliferates. The bacterium can form a biofilm, allowing it to adhere to metal implants. *C. acnes* is found in increased concentrations in the axillae, which can predispose to infection following shoulder surgery (6, 7). Several reviews have demonstrated that *C. acnes* is the most commonly isolated organism in periprosthetic infections following shoulder surgery and is a major cause of shoulder prosthesis failure (8, 9).

Current prophylaxis methods such as chlorhexidine gluconate or isopropyl alcohol are ineffective against *C. acnes*. Recent research has documented the greater effectiveness of peroxide-containing compounds in significantly reducing the incidence of *C. acnes* on the skin compared to current standard prophylaxis products. In addition, peroxide products have been shown to have bactericidal activity without developing antibiotic resistance. As the prevalence of shoulder joint prostheses continues to increase, understanding *C. acnes* and preventing infections caused by it is critical (10). However, there is no consensus regarding the recommended compound.

Therefore, we aimed to investigate and compare the effectiveness of the currently available antibacterial substances in shoulder surgery. We hypothesized that peroxide-containing preparations perform better than alcohol-based ones in reducing shoulder specific bacterial flora before shoulder surgery.

# Materials and methods

We have reported this network meta-analysis and systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement 2021 (Table 1). Our protocol was registered on PROSPERO under the registration number. Contrary to what is stated in the protocol, we did not have enough data to investigate dermis swabs and joint culture.

## Search strategy

A systematic search was conducted in MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) for studies published until October 2022, and selection was updated on January 20, 2025. The following search terms were used in all databases: 'shoulder' AND (*Cutibacterium* OR *Cutibacter* OR Propioni* OR '*C. acnes*' OR '*P. acnes*' OR acnes) AND (hydrogen OR hyperol OR HP OR H2O2 OR benzoyl OR benzil OR 'benzoyl-peroxide'). No restrictions were applied during the search. In addition, the reference lists of the included studies were screened for additional eligible articles.

## Eligibility criteria and selection strategy

The yield of the search was combined with the reference manager software (EndNote X9; Clarivate Analytics, USA). After the automatic and manual removal of duplicate records, two independent authors evaluated all studies' titles, abstracts, and full texts. First, we simultaneously performed a primary selection based on the title and abstract. Then, we assessed full texts for inclusion. Finally, a third author (GS) resolved disagreements.

We used the PICO framework to assess study eligibility. We included only randomized-controlled trials (RCTs) that investigated patients' shoulder skin (P) and compared different skin preparations (hydrogen peroxide – $H_2O_2$, 5% benzoyl peroxide – BPO 5%, 5% benzoyl peroxide with clindamycin – BPO 5% CLI, 5% benzoyl peroxide with miconazole-N – BPO 5% CLI MN, 10% benzoyl peroxide – BPO 10%, 3% hexachlorophene – pHisohex, chlorhexidine gluconate – CHG, and control). The outcomes (O) we examined were the reduced *C. acnes* culture in skin swabs, dermis swabs, and joint culture. Our study compared alcohol-based skin preparation with alcohol-based skin preparation supplemented with peroxide solutions. If there was less *C. acnes* outgrowth after skin treatment, this was considered a more favourable outcome. After sampling, the bacteria were cultured in anaerobic conditions for at least 12 days. Abstracts and grey literature (preprints and other non-peer-reviewed material) were excluded from the analysis.

## Data extraction

Two independent review authors (VW and BH) extracted data in duplicate into a standardized data collection form (Microsoft Excel 365, Microsoft Corporation, USA). Disagreements were resolved by a third party (GS). We used a standardized data collection sheet to collect all the necessary data: first author; publication year; study design; the clinical outcome was the skin dermis, and the joint culture after peroxide solution compared with the control group. A third party (GS) resolved discrepancies. The authors of the eligible articles were not contacted for further information.

## Statistical analysis

Primary data extraction and organization was carried out in Microsoft Excel. We performed a frequentist network meta-analysis to compare the effectiveness of different skin preparations in reducing *C. acnes* colonization. This approach allows the comparison of multiple interventions and the integration of direct and indirect evidence across a connected network of interventions. For each pairwise comparison, we calculated risk ratios (RRs) and their 95% confidence intervals (CIs) as the measure of effect

**Table 1** Basic characteristics of included studies.

| Study | Study site | Patients, *n* (male %) | Age, years* | Indication | Intervention | Control | Outcomes – skin/dermis/joint | Germ count |
|---|---|---|---|---|---|---|---|---|
| Grewal *et al.* (20) | USA | 60 (48) | 71.1 ± 7.1 vs 73.4 ± 9.8 | Primary arthroplasty | HPO | Standard skin preparation | Culture samples | Positive culture or not |
| Hancock *et al.* (23) | New Zealand | 22 (100) | Adults | Non-surgery, healthy volunteers | BPO | 2% CHG and alcohol | Before skin preparation, two swabs were taken from each shoulder region | Positive culture |
| Hsu *et al.* (22) | USA | 50 (100) | Adults | Shoulder arthroplasty | 10% BPO soap (BPO group) | 4% CHG solution (CHG group) | Skin surface swab, dermal edge swab | Positive culture, SpCuV |
| Kolakowski *et al.* (25) | USA | 80 (46) | Mean: 51 | Primary or revision shoulder surgery | 5% BPO | 4% CHG solution (CHG group) | Skin swab at the anterior, lateral, and posterior arthroscopic portal sites and the axilla | Positive culture |
| Scheer *et al.* (26) | Sweden | 40 (60) | 20–66 | Non-surgery, healthy volunteers | 5% BPO | 4% CHG solution (CHG group) | Before and after topical treatment, after surgical skin preparation and sterile draping | Positive culture |
| Vendela *et al.* (24) | Sweden | 100 (63) | Mean: 65/63 | Primary elective open shoulder surgery | 5% BPO | CHG | After surgical skin preparation, 1 in dermis, and finally after the skin was sutured. Before skin incision, 5 punch biopsies | Positive culture |
| Stull *et al.* (21) | USA | 70 (100) | 54.2 ± 13.4 vs 50.1 ± 13.2 | Shoulder arthroscopy | Additional with 3% HPO | Standard skin preparation | 3 mm punch biopsy was obtained from the posterior arthroscopic portal site of all patients | Positive culture |
| Symonds *et al.* (27) | Australia | 101 (60) | 68.1 ± 6.9; 70 ± 5.9; 67.9 ± 7.6 | Total shoulder arthroplasty | BPO/BPO + C | Phisohex solution | Swab1-skin, Swab2-skin, Swab3-dermis, Swab4-joint, Swab5-dermis, Swab6-surgical. Trolley | Positive culture |
| Unterfrauner *et al.* (28) | Switzerland | 60 (45) | 59 | Open-shoulder surgery | 5% BPO/2% MN | Standard skin preparation | Swab1-skin, Swab2-skin, Swab3-subcutaneous Swab4-capsule | Positive culture |
| Van Diek *et al.* (29) | Netherlands | 29 | 57.2 (8.6) | Healthy participants | 5% BPO | Placebo | Skin | Positive culture |

*Values presented as the mean with standard deviation, or median with range (minimum and maximum).

BPO, benzoil peroxide; BPO + C, benzoil peroxide plus clindamycin; HPO, hydrogen peroxide; MN, miconasole nitrate; CHG, chlorhexidine gluconate; SpCuV, specimen Cutibacterium value.


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size. We used a random-effects approach since we expected considerable between-study heterogeneity. The variance component was estimated using restricted maximum likelihood (REML). Multi-arm studies were included using multi-arm correction methods to ensure accurate variance estimates and avoid double-counting participants. Treatments were ranked using the P-score metric, which quantifies the certainty that an intervention is better than another based on point estimates and standard errors (11, 12, 13). Diagnostics for consistency and reliability included netsplit analysis, direct evidence proportion plots, minimal parallelism plots, and mean path length plots. These methods evaluated the robustness of the effect size estimates by distinguishing between direct and indirect evidence. Due to the limited number of studies, formal tests for publication bias, such as funnel plots, were not performed.

The results were visualized using forest plots (where interventions are compared to a reference, in our case: "none"), league tables (where the upper triangle shows direct pairwise comparisons, while the lower triangle shows the results of network meta-analysis), network graphs (where circles at the vertices represent intervention arms and edges represent direct comparisons), and rank plots (where treatments are ranked based on the aforementioned P-score metric), providing a comprehensive summary of the intervention comparisons. All analyses were performed in the R (version 4.4.1; 2024-06-14) using the {meta} (11, 13, 14) and {qgraph} packages (11, 14, 15, 16).

### Risk of bias (RoB) assessment

The RoB assessment was performed independently by two authors (VW and BH) using the RoB 2 tool for RCTs recommended by the Cochrane Collaboration. Disagreements were resolved by consensus. We used the robvis web app tool to visualize the RoB assessment (17).

### Certainty of evidence

The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group modality approach was used to assess the certainty of evidence. The certainty of the evidence was independently assessed by two authors (VW and BH), and disagreements were resolved by consensus (Supplementary Table 1 (see section on Supplementary materials given at the end of the article)).

## Results

### Search and selection

In total, 214 records were identified through electronic database searches, of which ten publications were included in our network meta-analysis (Fig. 1).

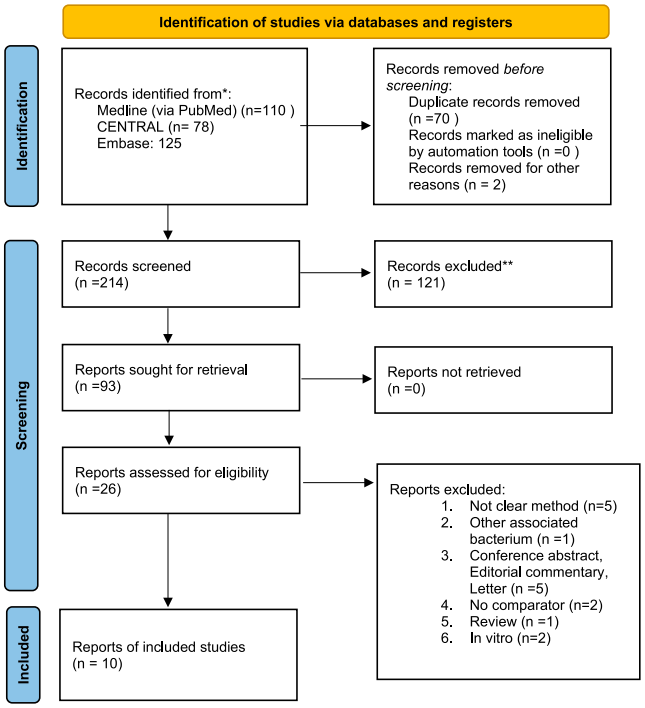


**Figure 1**

PRISMA 2020 flowchart representing the study selection process.

### Basic characteristics of included studies

All included studies were single-centre RCTs. Two of the ten articles compared the $H_2O_2$ with 4% CHG (18, 19). One of them compared the 10% BPO with 4% CHG (20) and three compared 5% BPO with the 4% CHG (21, 22, 23). One article compared the 5% BPO with regular soap (24). One article compared the 5% BPO with phisohex and 5% BPO + clindamycin (25). One article used 5% BPO plus MN (26), and one compared the 5% BPO with placebo (27).

A detailed description of the included studies is shown in Table 2. The network graph of the included publications' interventions is presented in Supplementary Fig. 1.

Our network meta-analysis compared the *C. acnes* reduction potential of different interventions. We considered the reducing effect of skin flora in our analysis. We did not have enough data on the dermis and articular bacterial flora to perform the analysis.

### Effectiveness of different interventions to eradicate *C. acnes* on the skin

In our network meta-analysis, we compared seven different interventions from ten different articles. In total, we examined 948 intervention events. Figure 2 shows the network graph with the total number of interventions, the number of comparisons, and the number of comparative studies. The forest plot (Fig. 3)

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**Table 2** League table. The intervention groups are presented in bold.

| V1 | V2 | V3 | V4 | V5 | V6 | V7 | V8 |
|---|---|---|---|---|---|---|---|
| **BPO10%** | | | | 1.00 (0.41; 2.45) | | | |
| 1.42 (0.44; 4.57) | **BPO5%** | 1.00 (0.23; 4.26) | | 0.71 (0.33; 1.50) | | 0.25 (0.08; 0.72) | 0.38 (0.11; 1.35) |
| 1.42 (0.22; 9.13) | 1.00 (0.23; 4.26) | **BPO5% CLI** | | | | | 0.38 (0.11; 1.35) |
| 0.44 (0.06; 2.95) | 0.31 (0.07; 1.39) | 0.31 (0.04; 2.50) | **BPO5% MN** | | | 0.80 (0.28; 2.30) | |
| 1.00 (0.41; 2.45) | 0.71 (0.33; 1.50) | 0.71 (0.14; 3.62) | 2.29 (0.42; 12.38) | **CHG** | 0.75 (0.14; 3.98) | | |
| 0.75 (0.11; 4.99) | 0.53 (0.08; 3.30) | 0.53 (0.05; 5.47) | 1.72 (0.16; 18.44) | 0.75 (0.14; 3.98) | **H2O2** | | |
| 0.35 (0.07; 1.71) | 0.25 (0.08; 0.72) | 0.25 (0.04; 1.50) | 0.80 (0.28; 2.30) | 0.35 (0.09; 1.30) | 0.47 (0.06; 3.89) | **None** | |
| 0.54 (0.10; 3.02) | 0.38 (0.11; 1.35) | 0.38 (0.11; 1.35) | 1.23 (0.17; 8.84) | 0.54 (0.12; 2.35) | 0.72 (0.08; 6.64) | 1.54 (0.29; 8.13) | **Phisohex** |

shows that 5% benzyl peroxide was the only intervention with a significant difference compared to the control group (RR = 0.25, CI: 0.08–0.72). 5% BPO, in addition to clindamycin, reduced the *Cutibacterium* flora of the skin on the same level. However, the difference was non-significant compared to the control (RR = 0.25, CI: 0.04–1.50). 5% BPO with MN showed the smallest difference compared to the control group (RR = 0.80, CI: 0.28–2.30).

Based on the rank plot (Fig. 4), 5% BPO (P score: 0.808) proved to be the most effective treatment, followed by BPO 5% plus CLI (P score: 0.749).

Based on the league table (Table 2), we could not find any other significant comparison.

## Effectiveness of different interventions to eradicate *C. acnes* on the dermis

Four articles reported on dermis samples (18, 20, 25, 26). There was no difference in the form of $H_2O_2$ intervention compared to the control group. When 10% BPO was used as an intervention, it reduced the number of *C. acnes* cultured in the dermis more than CHG as a control. In the article comparing BPO/BPO + CLI/phisohex, the best result for reducing dermis *C. acnes* was BPO applied in non-combination, but the combination with CLI also gave better results than the plain phisohex solution. BPO 5% supplemented with 2% MN reduced *C. acnes* better than no intervention ointment.

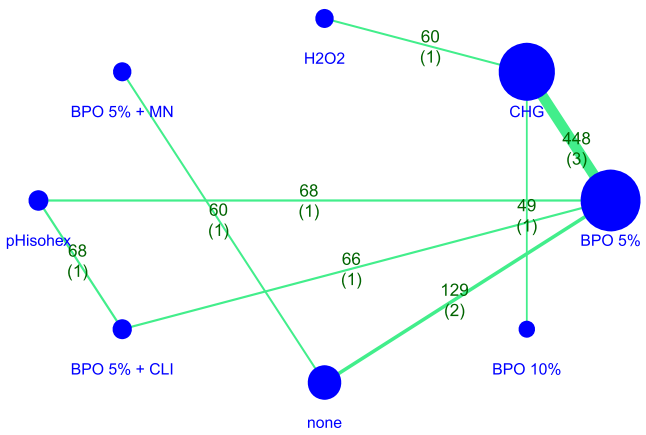


**Figure 2**

The network graph shows direct comparisons of different interventions.

## Effectiveness of different interventions to eradicate *C. acnes* in the joint

Three articles dealt with the joint sample (18, 25, 26). There was no difference in the samples taken for $H_2O_2$. In none of the cases did *C acnes* grow out of the joint. When 5% BPO and 5% BPO + CLI were tested, there were fewer cases of *C. acnes* colonization with these substances than with phisohex solution, but no difference between BPO in combination and BPO alone was found.

## Risk of bias assessment and certainty of the evidence

Most of the included articles were judged as low-to-moderate ('some concerns') RoB, except one article, which had a high RoB (due to 'bias in measurement in outcome'). A summary of the RoB assessment can be found in the supplementary material (Supplementary Figs 1 and 2).

The grade of evidence was of moderate or very low quality for each pairwise comparison between interventions.

# Discussion

Although *C. acnes* is often associated with surgical site infection following shoulder surgery, it is largely unaffected by standard preoperative skin disinfectants. Our research has shown that BPO significantly reduces *C. acnes* bacterial counts and that 5% BPO was the best count-reducing treatment for this.

The diagnosis and treatment of *C. acnes* can be particularly challenging. The literature suggests that adding peroxide-containing agents to current prophylaxis methods can significantly reduce the number of *C. acnes* copies compared to standard chlorhexidine preparations

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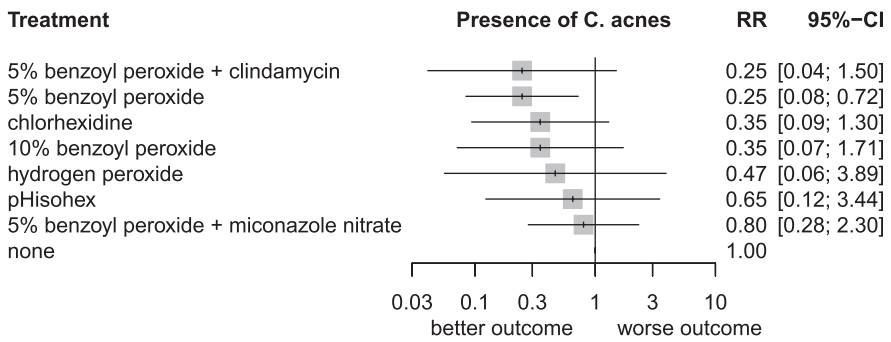


**Figure 3**

Forest plots representing the odds of the positive *C. acnes* culture on skin.

(19, 22, 27, 28, 29, 30). However, the results are still inconsistent, and we conducted our study to resolve this inconsistency.

Numerous studies incorporated a 5% BPO concentration. Scheer *et al.* conducted an investigation comparing the application of 5% BPO five times to the standard three-time application of 4% CHG. Their results indicated that using 5% BPO significantly decreased the presence of *C. acnes* after preoperative preparation (22, 31). Van Diek *et al.* showed a significant reduction in the presence of *C. acnes* on the skin of the shoulder after BPO compared to placebo. The BPO application involved treating the entire shoulder and axilla region five times, commencing 48 h before the surgical procedure (27, 31). Kolakowski and colleagues also demonstrated a reduction in colonization units when 5% BPO gel was applied a few days before surgery compared to CHG. They showed that applying BPO three times daily resulted in a significant reduction in *C. acnes* bacterial load on the anterior and posterior portals compared to the daily application of CHG. They used a technique that allowed for the quantification of *C. acnes* in sebaceous glands, suggesting that benzoyl peroxide is better able to penetrate deeper layers than chlorhexidine gluconate, which previous studies have

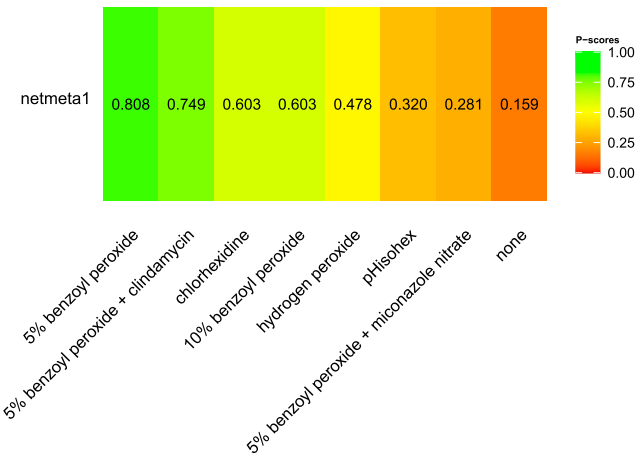


**Figure 4**

Rank plots representing the most effective material to reduce the *C. acnes* culture on skin.

shown to be ineffective in eradicating *C. acnes* from the skin (23, 31). BPO reduced *C. acnes* on the shoulder more effectively than chlorhexidine (23, 29).

In contrast to the above studies, Hancock and colleagues found that a single application at the time of surgery does not reduce *C. acnes*. Their research suggests that multiple applications before the day of surgery are necessary to reduce the burden. This may be because *C. acnes* tends to reside in the pilosebaceous glands (21). Similarly, Hsu *et al.* investigated the use of 10% BPO soap applied before surgery compared to CHG, which showed no reduction in *C. acnes* before standard preparation (20, 31).

The combination of BPO with clindamycin has been shown in several studies in the dermatological literature to reduce the colonisation of *C. acnes* (19, 29, 32). The combination of these agents, by penetrating the deep dermal layer, provides a potent local antimicrobial prophylaxis and inhibits the development of antibiotic resistance. This combination was found to have the same efficacy as BPO 5% alone; however, the effect was not statistically significant.

Dizay *et al.* showed a reduction in deep tissue *C. acnes* bacterial load in patients who received daily BPO and clindamycin cream combination therapy for an average of 2–3 days (25, 29). Topical BPO and benzoyl peroxide with clindamycin has been shown to reduce the bacterial load of *C. acnes* on the skin.

$H_2O_2$ has also been shown to be effective in reducing the copy number of *C. acnes*, as Stull *et al.* showed that the addition of hydrogen peroxide to preoperative surgical skin preparation significantly reduces the culture rate of *C. acnes* in the shoulder in the perioperative period (19, 31).

Another topical agent is miconazole nitrate (MN), a broad-spectrum imidazole derivative that interferes with lipid synthesis and *C. acnes* membrane permeability. In this way, the synergistic MN promotes the penetration of BPO into bacterial cells and ultimately supports improved tolerability of topical combination therapy.

In treating acne vulgaris, BPO and MN cream effectively reduce the superficial *C. acnes* load on the skin (26).

From the above and our overall results, it can be concluded that adding BPO can successfully reduce the copy number

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of *C. acnes* on the skin before shoulder surgery. Reducing the germ count of *C. acnes* can reduce intraoperative wound infection and postoperative infection. BPO should be considered an adjunctive preoperative modality, given its potential benefits, low risk, and low cost.

## Strengths and limitation

Regarding the strengths of our study, the study utilized a network meta-analysis, which evaluated multiple dermal solutions' efficacy in reducing *C. acne* flora before shoulder surgeries. This method thoroughly compared various interventions, providing valuable insights into their relative effectiveness. Including RCTs ensured a higher level of evidence in the study. Our study was registered on PROSPERO, ensuring transparency.

On the other hand, our study has several limitations. The finding that only one intervention showed a statistically significant difference compared to the control may indicate a lack of consistent and strong evidence for the efficacy of the evaluated dermal solutions. This could be due to the limited number of eligible RCTs or variations in study design and patient populations. The inability to test for publication bias might introduce the possibility of selective reporting of positive outcomes, potentially skewing the overall conclusions. The observed heterogeneity in the outcomes of the included studies may limit the ability to draw definitive conclusions. Variability in study designs, patient characteristics, and intervention protocols could contribute to this heterogeneity. The focus solely on *C. acnes* eradication from the skin, not from the dermis or the joint, might limit the study's applicability to the broader context of shoulder surgeries.

## Implication for practice and research

By supplementing alcohol-based skin disinfectants with peroxide-containing agents, we have a good chance of reducing the incidence of septic complications, the most dreaded in orthopaedic surgery.

In addition, further research with a broader range of outcomes and more standardized protocols may be needed to strengthen the evidence in this field. It is recommended that the skin surface, dermis, and intra-articular cultures be investigated, taking into account different time frames. Surgical outcomes should also be evaluated. Finally, the rapid application of scientific results is of utmost importance (33, 34).

# Conclusion

Based on our network meta-analysis, we can conclude that the most effective agent to reduce the colonization of skin surface *C. acnes* is 5% BPO.

**Supplementary materials**

This is linked to the online version of the paper at https://doi.org/10.1530/EOR-2024-0160.

**ICMJE Statement of Interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work reported.

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**Data availability**

The datasets used in this study can be found in the full-text articles included in the systematic review and meta-analysis.

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