Arthrex ACP® Double-Syringe System in Knee Osteoarthritis

Scientific Information on Unapproved Uses for Cleared Products

RANDOMIZED CONTROLLED TRIALS WITH A POSITIVE OUTCOME

Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis.

Cerza F, Carnì S, Carcangiu A, Di Vavo I, Schiavilla V, Pecora A, De Biasi G, Ciuffreda M.

Patients: 120 **Follow-up: 2 years** **Treatments: ACP vs HA**

Purpose

The primary objective of this study was to compare the clinical response to hyaluronic acid (HA) and autologous conditioned plasma (ACP) treatment in 2 groups of patients with gonarthrosis grades I-III. The secondary objective was to evaluate whether there is any difference in clinical response between the two groups in relation to the grade of gonarthrosis.

Methods

A total of 120 patients affected by clinically and radiographically documented gonarthrosis were included in this study. The gonarthrosis was graded using the Kellgren-Lawrence radiographic classification scale. The 120 patients were randomized into 2 study groups in a 1:1 ratio: 60 patients received 4 intra-articular injections of PRP (specifically, ACP, 5.5 mL), and 60 patients received 4 intra-articular injections of HA (20 mg/2 mL). An unblinded physician performed infiltration once a week for 4 weeks into the knee affected by clinically relevant gonarthrosis (in both groups). All patients were evaluated with the Western Ontario and McMaster (WOMAC) score before the infiltration and at 4, 12, and 24 weeks after the first injection.

Results

- Treatment with a local injection of ACP had a significant effect shortly after the final infiltration and a continuously improving sustained effect up to 24 weeks (WOMAC score, 65.1 and 36.5 in the HA and ACP groups, respectively; $P < .001$), with better clinical outcomes compared with HA.
- In the HA group, the worst results were obtained for grade III gonarthrosis, whereas the clinical results obtained in the ACP group did not show any statistically significant difference in terms of the grade of gonarthrosis.
- The mean WOMAC scores for grade III gonarthrosis were 74.85 in the HA group and 41.20 in the ACP group ($P < .001$).

Limitations

Statistical analysis produced significant values. The subgroup of grade III gonarthrosis showed noteworthy differences, although it was of limited importance given the small number of patients with this grade of gonarthrosis in our series. Other limitations consisted of a relatively short-term follow-up and a lack of blinding.

Conclusion: Treatment with ACP showed a significantly better clinical outcome than HA, with sustained lower WOMAC scores. Treatment with HA did not seem to be effective in patients with grade III gonarthrosis.

Am J Sports Med. 2012;40(12):2822-2827. doi:10.1177/0363546512461902

Conflicts of interest: The authors declare no conflicts of interest.

Does intraoperative application of leukocyte-poor platelet-rich plasma during arthroscopy for knee degeneration affect postoperative pain, function and quality of life? A 12-month randomized controlled double-blind trial.

Duif C, Vogel T, Topcuoglu F, Spyrou G, von Schulze Pellengahr C, Lahner M.

Patients: 58 **Follow-up: 12 months** **Treatments: ACP vs no ACP (intraoperatively)**

Purpose

The study aimed to identify the effects of intraoperatively applied leukocyte-poor platelet-rich plasma (LP-PRP; Arthrex ACP® system) during knee arthroscopy for degenerative lesions involving pain, function, and quality of life. Twenty-four patients were allocated to the LP-PRP group, and 34 to the control group. Ninety-one percent of enrolled patients were available for 12-month follow-up.

Methods

A randomized controlled, double-blind trial (RCT) including 58 patients for arthroscopic knee surgery for cartilage or meniscal degeneration with allocation into the LP-PRP (n = 24) or control group (n = 34) was conducted. During arthroscopy, LP-PRP was injected intra-articularly in the intervention group. At baseline, 6 weeks, 6 months, and 12 months, pain, function, and quality of life were assessed.

Results

- Pain was significantly lower in the LP-PRP group (VAS score of 0.9 vs 2.3) at 6 months, but not at 12 months VAS score of 1 vs 1.6).
- LP-PRP application improved the Lysholm score at 6 months (77.5 vs 65.6) and 12 months (83.2 vs 70). Assessment of quality of life (SF-36) for the physical component summary was significantly higher at 6 weeks (33.9 vs 25.6) and 6 months (29.9 vs 27.1) in the LP-PRP group, but equal at 1 year (31.4 vs 30.1).

Limitations

The study has several limitations. Due to unequal randomization and desired power not being achieved at the 6-month VAS even though post-hoc analysis showing a power of 0.86 this study was only categorized as a Level II RCT. The follow-up examination was restricted to 12 months due to the temporary effect of PRP, which may leave potential long-term effects undetected. The platelet or leukocyte concentration was not analyzed to characterize and quantify the PRP formulations because of the direct preparation inside the OR using the Arthrex ACP double-syringe technique with immediate application. The outcome measures focused on patient-related aspects but lacked objective parameters, such as IL-6, sonographically assessed volume of effusion, or range of motion.

> **Conclusion:** Intraoperative application of LP-PRP may enhance pain reduction and improve knee function within 6-12 months compared to arthroscopy alone.

Arch Orthop Trauma Surg. 2015;135(7):971-977. doi:10.1007/s00402-015-2227-5

Conflicts of interest: The authors declare no conflicts of interest.

Hyaluronic acid versus platelet-rich plasma: a prospective, double-blind randomized controlled trial comparing clinical outcomes and effects on intra-articular biology for the treatment of knee osteoarthritis.

Cole BJ, Karas V, Hussey K, Pilz K, Fortier LA.

Patients: 111 **Follow-up: 2 years** **Treatments: ACP vs HA**

Purpose

The study aimed at comparing the clinical and biological effects of an intra-articular injection of Arthrex ACP® PRP with those of an intra-articular injection of HA in patients with mild to moderate knee osteoarthritis (OA). Forty-nine patients were randomized to receive treatment with PRP, and 50 patients were randomized to receive treatment with HA. Patients received 3 weekly ultrasound-guided intra-articular injections.

Methods

A total of 111 patients with symptomatic unilateral knee OA received a series of either leukocyte-poor PRP or HA injections under ultrasound guidance. Clinical data were collected before treatment and at 4 time points across a 1-year period. Synovial fluid was also collected for analysis of proinflammatory and anti-inflammatory markers before treatment and at 12 and 24 weeks after treatment.

Several measures were used to assess results: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale; International Knee Documentation Committee (IKDC) subjective knee evaluation; visual analog scale (VAS) for pain; Lysholm knee score; and differences in intra-articular biochemical marker concentrations.

Results

- There were 49 patients randomized to treatment with PRP and 50 randomized to treatment with HA.
- No difference was seen between the groups in the primary outcome measure (WOMAC pain score).
- In the secondary outcome measure, linear contrasts identified a significantly higher IKDC score in the PRP group compared with the HA group at 24 weeks (mean ± standard error [SE], 65.5 ± 3.6 vs 55.8 ± 3.8, respectively) and at final follow-up (52 weeks) (57.6 ± 3.37 vs 46.6 ± 3.76, respectively).
- Linear contrasts also identified a statistically lower VAS score in the PRP group than in the HA group at 24 weeks (mean ± SE, 34.6 ± 3.24 vs 48.6 ± 3.7, respectively; $P = .0096$) and 52 weeks (44 ± 4.6 vs 57.3 ± 3.8, respectively).
- An examination of fixed effects showed that patients with mild OA and a lower body mass index had a statistically significant improvement in outcomes.
- In the biochemical analysis, differences between groups approached significance ($P = .06$) for IL-1β (mean ± SE, 0.14 ± 0.05 pg/mL [PRP] vs 0.34 ± 0.16 pg/mL [HA]; $P = .06$) and tumor necrosis factor-α (TNF-α) (0.08 ± 0.01 pg/mL [PRP] vs 0.2 ± 0.18 pg/mL [HA]; $P = .068$) at 12-week follow-up.

Limitations

A limitation of this study is the lack of a sham control group and a comparison with corticosteroids. A large randomized controlled trial including a sham control, corticosteroid injection, HA injection, and PRP injection is of great interest. Additionally, there was a significant difference of 2 BMI points between the patient groups. Despite this difference, both groups were characterized as ''overweight'' according to the CDC classification (BMI, 25.0-29.9 kg/m^2). All statistical analyses were conducted using a mixed-effects model that included BMI, Kellgren-Lawrence (KL) grade, age, preoperative pain, and sex as fixed effects. The final limitation is that the power analysis was based solely on patient-reported outcomes due to the paucity of data on changes in intra-articular biology over time with treatment. Future studies are warranted to use the data presented herein for a power analysis based on biological outcomes.

> **Conclusion:** No difference was found between HA and Arthrex ACP PRP at any time point in the primary outcome measure: the patient-reported WOMAC pain score. Significant improvements were seen in other patient-reported outcome measures, with results favoring PRP over HA. Preceding a significant difference in subjective outcomes favoring ACP, there was a trend toward a decrease in 2 proinflammatory cytokines, which suggests that the anti-inflammatory properties of PRP may contribute to an improvement of symptoms.

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Intra-articular autologous conditioned plasma injections provide safe and efficacious treatment for knee osteoarthritis: an fda-sanctioned, randomized, double-blind, placebo-controlled clinical trial.

Smith PA.

Patients: 30 **Follow-up: 1 year** **Treatments: ACP vs saline placebo**

Purpose

The study aimed to determine the safety and efficacy of LP-PRP ACP for knee OA treatment through a feasibility trial regulated by the US Food and Drug Administration (FDA). Fifteen patients received ACP, and 15 received a saline placebo.

Methods

In accordance with FDA protocol, patient selection was based on strict inclusion/exclusion criteria; 114 patients were screened, and 30 were ultimately included in the study. These patients were randomized to receive either ACP (n = 15) or saline placebo (n = 15) for a series of 3 weekly injections. WOMAC scores served as the primary efficacy outcome measure. Patients were followed for 1 year.

Results

- No adverse events were reported for ACP administration.
- Furthermore, the results demonstrated no statistically significant difference in baseline WOMAC scores between the two groups. However, in the ACP group, WOMAC scores at 1 week were significantly decreased compared with baseline scores, and the scores for this group remained significantly lower throughout the study duration.
- At the study conclusion (12 months), subjects in the ACP group had improved their overall WOMAC scores by 78% from their baseline score, compared with 7% for the placebo group.

Limitations

One potential limitation of the current study relates to the small sample size mandated by the FDA. However, these concerns were resolved by the statistically significant outcomes for the ACP treatment group, in that all 15 patients had major improvement by an average of 78% from their baseline WOMAC score. Additionally, these concerns were alleviated after the post hoc power analysis demonstrated that the sample size was adequate. Another potential limitation in this study could be the use of saline as a placebo control instead of HA or steroids. The FDA, however, mandated a saline placebo to create a realistic baseline for comparing the effects of ACP. Despite this requirement, it might be inferred that the use of saline would give an unfair advantage to ACP in terms of showing efficacy. In that regard, it is important to evaluate other trials using a saline placebo, particularly against HA.

> **Conclusion:** The primary objective of the current study was to determine the safety of ACP, and the secondary objective was to determine the efficacy of ACP in patients with primary OA of the knee. Arthrex ACP® PRP is safe and provides quantifiable benefits for pain relief and functional improvement with regard to knee OA. No adverse events were reported for ACP administration. After 1 year, WOMAC scores for the ACP subjects had improved by 78% from their baseline score, whereas scores for the placebo control group had improved by only 7%. Other joints affected with OA may also benefit from this treatment.

Am J Sports Med. 2016 Apr;44(4):884-91. doi: 10.1177/0363546515624678.

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Platelet-rich plasma is similar to platelet-rich plasma plus hyaluronic acid for the treatment of knee osteoarthritis at 2 years: a randomized controlled trial.

Branch EA, Cook JJ, Cohen A, Plummer H, Emami A, Truett J, Anz AW.

Patients: 29 **Follow-up: 24 months** **Treatments: ACP vs ACP with HA**

Purpose

The primary objective of this study was to determine if HA injected with ACP would improve the efficacy of treatment of symptomatic knee OA compared to ACP alone. It was hypothesized that the addition of HA would improve the efficacy of ACP.

Methods

A total of 64 participants with KL grades 1-4 knee OA were randomized into 2 groups and scheduled to receive 3 injections. Group 1 received injections of Arthrex ACP® PRP. Group 2 received the same treatment, with an additional HA injection for the first 2 injections. Both groups were blindfolded for the first 2 injections. To evaluate the efficacy of the regimen, participants completed patient-reported outcome measures (PROMs). PROMs were completed prior to injections and at 1, 3, 6, 12, 18, and 24 months after the final injection.

Results

- Participants in both groups felt pain consistent with standard-of-care HA injection regimens, with no difference in perceived pain.
- No infections or complications were observed.
- All PROM scores demonstrated improvement over baseline from 1-24 months postinjections.
- There were no statistically significant differences between the groups.

Limitations

The limitations of this study include the lack of a true placebo group, only measurement of clinical symptomatology without radiological evidence, lack of KL grade comparisons, and underpowered PROMs. This study did not include a true placebo group, such as the use of a saline injection, because several studies have already compared HA and PRP separately to a true placebo, as well as intragroup comparisons. Due to this, our findings should be compared to the available historical data of other studies that involved true placebos, although we do recognize that this external requirement is a limitation of our study. Future studies should capture both PROMs and measure improvement radiologically or by objective, quantitative methods. Additionally, the efficacy of treatment may differ in mild KL grades 1-2 compared to KL grades 3-4, but this study did not have a large enough distribution of KL grades to study this further. Finally, the study was appropriately powered and designed for WOMAC as the primary outcome measure through 12 months postinjection series, but is underpowered past 12 months due to compliance issues. A power analysis was not performed for the IKDC and KOOS, so it is likely that these PROMs are underpowered and were treated as such during the study.

> **Conclusion:** For the treatment of OA, PRP alone or PRP concomitantly with HA performed similarly out to 24 months. PRP in combination with HA was not superior to PRP alone.

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Conflicts of interest: The authors declare no conflicts of interest.

RANDOMIZED CONTROLLED TRIALS WITH A NEUTRAL OUTCOME

Double-blind randomized controlled trial comparing platelet-rich plasma with intra-articular corticosteroid injections in patients with bilateral knee osteoarthritis.

Pretorius J, Nemat N, Alsayed A, Mustafa A, Hammad Y, Shaju T, Nadeem S.

Patients: 29 | **Follow-up: 6 months** | **Treatments: ACP vs methylprednisolone**

Purpose

This study aimed to assess whether ACP intra-articular injections are more effective than steroid injections in treating patients with mild-to-moderate knee OA in relation to pain, stiffness, and function.

Methods

A double-blind randomized controlled trial including 29 patients (58 knees) with radiologically confirmed mild-to-moderate bilateral knee osteoarthritis was conducted. They were randomized to receive an intra-articular ACP injection into one knee and a methylprednisolone injection with a local anesthetic into the contralateral knee. The primary outcome was measured using WOMAC at baseline and at 6 weeks, 3 months, and 6 months posttreatment. The secondary outcome was measured pain with the visual numerical pain rating scale (VNS).

Results

- Corticosteroids and PRP were both effective in improving pain, stiffness, and function at all time points, with maximal improvements at six weeks and three months.
- PRP scored slightly better than steroid injections at 6 months; nevertheless, there was no statistically significant difference between corticosteroids and PRP injections ($F_{2,139} = 0.168$, $P = .85$).
- The secondary outcome also delivered the same result with improvement at all time points but no statistically significant difference ($F_{2,139} = 0.168$, $P = .85$).

Limitations

This study has several limitations. First, the study included a small sample size and had a short-to-mid-term follow-up period. Another limitation is that injections were not administered under ultrasound guidance, although all injections were administered by two experienced orthopedic doctors using a standardized technique. One of this study's greatest benefits could also be considered a limitation, namely, using the patients' own contralateral knees as their own control group. This removed the interpersonal variations between different patients with regard to patient demographics and comorbidities. However, there is a possibility that a carryover effect may occur between the two knees, as patients may inadvertently compare one knee to the other when reporting pain, stiffness, and function using the WOMAC as well as VAS scoring systems.

> **Conclusion:** Both corticosteroids and PRP interventions are effective in improving pain, stiffness, and function in patients with bilateral knee osteoarthritis up to 6 months with no statistically significant difference between the two.

Cureus. 2022;14(9):e29744. doi:10.7759/cureus.29744

Conflicts of interest: The authors declare no conflicts of interest.

Intra-articular infiltration of platelet-rich plasma versus hyaluronic acid in patients with primary knee osteoarthritis: preliminary results from a randomized clinical trial.

Arliani GG, Durigon TS, Pedroso JP, Ferreira GF, Oksman D, Oliveira VO.

Patients: 29 **Follow-up: 6 months** **Treatments: ACP vs HA**

Purpose

The study aimed to compare the effects of intra-articular infiltration of ACP with those of hyaluronic acid infiltration in the treatment of patients with primary knee osteoarthritis.

Methods

A randomized clinical trial was conducted with 29 patients who received an intra-articular infiltration with hyaluronic acid (control group) or ACP. Clinical outcomes were assessed using VAS for pain and WOMAC questionnaire before and after the intervention. Additionally, posttreatment adverse effects were recorded. Categorical variables were analyzed using the chi-square and Fisher's exact tests, whereas continuous variables were analyzed using the Student *t* test, analysis of variance, and the Wilcoxon test; all calculations were performed using the Stats package of the R software.

Results

- An independent analysis of each group revealed a statistical difference in the first months, with improvement in the pain and function scores, but worsening in the sixth month after the procedure.
- There was no difference in the outcomes between the groups receiving hyaluronic acid or ACP.
- There was no serious adverse effect or allergic reaction during the entire follow-up period.

Limitations

The study has some limitations. First, despite being a preliminary report, the sample size is small. Second, the follow-up period is relatively short (6 months), and some studies have shown that ACP effects last longer than those of HA. The absence of a sham group (placebo or steroid infiltration) and the lack of group blinding are other limitations of the study.

> **Conclusion:** Knee intraarticular infiltration with HA or ACP in patients with primary gonarthrosis resulted in transient improvement of pain and function. Both treatments proved to be safe. There was no difference between these interventions.

Rev Bras Ortop (Sao Paulo). 2021;57(3):402-408. doi:10.1055/s-0041-1724082

Conflicts of interest: The authors declare no conflicts of interest.

RANDOMIZED CONTROLLED TRIALS WITH A NEGATIVE OUTCOME

A randomized trial of intra-articular injection therapy for knee osteoarthritis.

Tschopp M, Pfirrmann CWA, Fucentese SF, Brunner F, Catanzaro S, Kühne N, Zwyssig I, Sutter R, Götschi T, Tanadini M, Rosskopf AB.

Patients: 120 **Follow-up: 6 months** **Treatments: Glucocorticoid vs HA vs ACP vs placebo**

Purpose

The aim of this study was to compare clinical outcomes after intra-articular injections of glucocorticoid, hyaluronic acid, ACP, or placebo in patients with mild or moderate OA of the knee.

Methods

In a double-blinded, placebo-controlled, single-center trial, knees with early- to middle-stage knee OA (KL grades 1-3) were randomly assigned to an intra-articular injection with one of these substances: glucocorticoid, hyaluronic acid, ACP, or placebo. The primary outcome was pain reduction within 6 months after the injection, assessed with the numeric rating scale (NRS; range, 0-100). Secondary outcome parameters included WOMAC scores, Tegner Activity Scale, knee mobility, and adverse events. Finally, a linear mixed-effects model was calculated and corrected for possible patient and covariate effects.

Results

- One hundred twenty knees (30 knees per treatment group) in 95 patients (41 female) were included in the final analysis.
- The median age of patients was 60 years (interquartile range, 54-68). There was no evidence that the drug effects of primary and secondary outcome parameters differed over time.
- The median pain at baseline was 32.5 (interquartile range, 15-50) on NRS.
- The changes in pain level during the first 6 months compared with baseline were small (within ± 5 points on NRS), whereas the intrapatient variability was large between −20 and +20 points.
- Secondary outcome parameters did not differ significantly among the groups. KL grade did not have a statistically significant effect on pain reduction (P = .61).

Limitations

Up to now, there is no clear recommendation on how often ACP should be injected. Because of the blinded study design, multiple PRP injections could not be offered to the patients. The study included patients with 1 or 2 knees treated. This was taken into account in the statistical modeling, and a model with 2 random effects (for the patient and the patient's knee) and an additional variable predictor that accounts for the treatment applied to the contralateral knee was implemented. Because systemic effects of glucocorticoid injections have only been reported up to 1 month after the initial injection, the second knee was injected at least 3 months after the injection in the contralateral knee. Lastly, intra-articular injections are known for a strong placebo effect. Self-reported parameters such as pain and stiffness are susceptible to this phenomenon. Future studies with larger study cohorts are warranted to confirm the findings.

> **Conclusion:** There is no evidence that knee injections with glucocorticoid, PRP, or hyaluronic acid have superior short- or long-term effects in patients with low pain level at baseline and early- to middle-stage knee OA when compared with placebo.

Invest Radiol. 2023;58(5):355-362. doi:10.1097/RLI.0000000000000942

Conflicts of interest: The authors declare no conflicts of interest. Data generated or analyzed during the study and the study protocol are available from the corresponding author by request.

The effectiveness of leucocyte-poor platelet-rich plasma injections on symptomatic early osteoarthritis of the knee: the PEAK randomized controlled trial.

Lewis E, Merghani K, Robertson I, Mulford J, Prentice B, Mathew R, Van Winden P, Ogden K.

Patients: 102 | **Follow-up: 12 months** | **Treatments: ACP vs ACP and saline placebo vs saline placebo**

Purpose

Platelet-rich plasma (PRP) intra-articular injections may provide a simple and minimally invasive treatment for early-stage knee osteoarthritis (OA). This has led to an increase in its adoption as a treatment for knee OA, although there is uncertainty about its efficacy and benefit. It was hypothesized that patients with early-stage symptomatic knee OA who receive multiple ACP injections would have better clinical outcomes than those receiving single PRP or placebo injections.

Methods

A double-blinded, randomized, placebo-controlled trial was conducted with three groups: one receiving placebo injections (normal saline), one receiving one ACP injection followed by two placebo injections, and another receiving three ACP injections. Each injection was given 1 week apart. Outcomes were prospectively collected prior to intervention and then at 6 weeks, 3 months, 6 months, and 12 months post-intervention. Primary outcome measures were the Knee Injury and Osteoarthritis Outcome Score (KOOS) and EuroQol five-dimension five-level index (EQ-5D-5L). Secondary outcomes included VAS for pain and patient subjective assessment of the injections.

Results

- A total of 102 patients were recruited. The follow-up period was 12 months, at intervals of 6 weeks, 12 weeks, 6 months, and 12 months.
- KOOS total significantly improved in all groups at these time intervals compared to pre-injection.
- There was an improvement in EQ-5D-5L index scores in saline and single injection groups, but not in the multiple injection group.
- Comparison of treatment groups showed no additional beneficial effect of single or multiple ACP injections above that displayed in the saline injection group.
- Subjective patient satisfaction and recommendation of treatment received demonstrated a similar pattern in all the groups.
- There was no indication of superiority of either single or multiple ACP injections compared to saline injections.

Limitations

To date, no universal nomenclature has been established for PRP classification. Outcomes reported in this study relate to the leucocyte-poor ACP subtype of PRP injections. As such, these effects may not be predictive of outcomes using other PRP formulations. This is a notable limitation in this study and broader literature, as has been recently recognized. A further limitation is the lack of specific component analysis of the PRP product produced. Additionally, the study has several further limitations. A controlled no-treatment group would have been helpful to describe the natural history of the disease, map the natural fluctuations in pain scores that this cohort of patients can display, and refute the argument that saline has therapeutic effects. However, the addition of such a group was not possible in the setting of a patient-blinded study design. As stated, the sample size was inadequate for a clear demonstration of superiority, and demonstrating non-inferiority would have been even more challenging. It is not possible to demonstrate correlation with optimum orthobiologic therapeutic effectiveness standards. Finally, data regarding the exercise and physiotherapy programs undertaken by the involved patients were not collected, which may contribute to the heterogeneity of the results.

> **Conclusion:** There is no evidence that single or multiple PRP had any additional beneficial effect compared to saline injection up to 12 months' follow-up after treatment of early stage symptomatic OA of the knee.

Bone Joint J. 2022;104-B(6):663-671. doi:10.1302/0301-620X.104B6.BJJ-2021-1109.R2

Conflicts of interest: The authors declare no conflicts of interest.

OUTCOME DEFINITIONS

Outcome	Definition
Positive	A positive outcome is defined as a significant improvement of the treatment group of interest compared to the comparison group (control, placebo, or other treatment) or the pretreament condition in one or more primary or secondary outcome measures. A positive outcome can also be assigned to a study describing an equivalent outcome in combination with other benefits described by the authors.
Neutral	A neutral outcome is defined as no significant difference between the treatment group of interest and the comparison group (control, placebo, or other treatment) in any primary or secondary outcome measures, and no additional medical benefit is reported by the authors.
Negative	A negative outcome is defined as a significantly worse result in the treatment group of interest compared to another treatment group or no improvement compared to the pretreatment condition, control, or placebo group in one or more primary or secondary outcome measures. The outcome is also assessed as negative when the authors make a negative conclusion or report additional medical risks or adverse events associated with the treatment.