Inflammatory arthritis or osteoarthritis of the knee – Efficacy of intra-joint infiltration of methylprednisolone acetate versus triamcinolone acetonide or triamcinolone hexacetonide

Artrite inflamatória ou osteoartrite de joelho – Eficácia da infiltração intra-articular de acetato de metilprednisolona versus triancinolona acetonida ou triancinolona hexacetonida

Authorship: Brazilian Medical Association (AMB)

Participants: Antonio Silvinato[1], Wanderley Marques Bernardo[1]

Final draft: June 27, 2017

[1]Associação Médica Brasileira (AMB)

http://dx.doi.org/10.1590/1806-9282.63.10.827

The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize procedures to assist the reasoning and decision-making of doctors.
The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

Grades of recommendation and levels of evidence

- **A:** Experimental or observational studies of higher consistency.
- **B:** Experimental or observational studies of lower consistency.
- **C:** Cases reports (non-controlled studies).
- **D:** Opinion without critical evaluation, based on consensus, physiological studies or animal models.

Objective

The objective of this evaluation is to provide, based on primary studies, the best current evidence on the efficacy and safety of intra-articular infiltration of methylprednisolone acetate, triamcinolone acetonide and triamcinolone hexacetonide in the treatment of inflammatory arthritis and osteoarthritis of the knee.

Description of evidence collection method

This guideline followed the standard of a systematic review with evidence retrieval based on the EBM (evidence-based medicine), so that clinical experience is integrated with the ability to critically analyze and apply scientific information rationally, thus improving the quality of medical care.

We used the structured mode of formulating questions synthesized by the acronym PICO, where P stands for adult patients with knee inflammatory arthritis or osteoarthritis, I stands for single infiltration with methylprednisolone acetate, C refers to comparison with triamcinolone acetonide or triamcinolone hexacetonide, and O stands for outcome (pain, function, and adverse events).

Based on the structured question, we identified the descriptors that formed the basis of the search for evidence in the databases: Medline-Pubmed. Thus, 20 studies were selected by title and five were chosen, after eligibility criteria evaluation (inclusion and exclusion), for answering the clinical questions (Annex I).

Clinical question

What is the efficacy and harm of methylprednisolone acetate compared to triamcinolone acetonide or triamcinolone hexacetonide in the treatment of inflammatory arthritis and osteoarthritis of the knee?

Introduction

Several studies have suggested good efficacy and safety of intra-articular (IA) injections of corticosteroids (CS) among children and adults to treat diseases such as inflammatory arthritis, osteoarthritis (OA), rotator cuff syndrome, epicondylitis, and carpal tunnel syndrome.[1-3]

Osteoarthritis is the most common chronic joint disease in the world.[4] It is a degenerative disease that affects joint cartilage leading to joint pain, stiffness, swelling and dysfunction. It has a multifactorial etiology (age,

obesity, trauma, poor alignment and genetics).[5] The joint most commonly affected by osteoarthritis is the knee, and the literature shows that more than 10% of men and more than 13% of women suffer from this degenerative disease.[6] Intra-articular steroids are a good alternative for patients with osteoarthritis.

Rheumatoid arthritis (RA) is a chronic inflammatory disease that mainly involves diarthrodial joints. Intra-articular injections of glucocorticoid (GC) have been used for more than half a century in the treatment of refractory synovitis in RA patients. There are limited data on the effectiveness of intra-articular injection of various preparations of GCs in inflamed joints.[7]

Selected evidence results

Two randomized clinical trials (RCTs)[8,9] (**B**) assessed the use of methylprednisolone acetate (MA) in patients with rheumatoid arthritis, comparing it with triamcinolone acetonide (TA) and triamcinolone hexacetonide (TH).

The first[8] (**B**) randomized 100 patients aged between 18 and 65 years with rheumatoid arthritis (n=89) or spondyloarthrosis (n=11), and who had a significantly swollen knee joint (defined as duration ≥ 1 week and < 24 weeks). Those who had received steroid infiltration in the same joint within the last three months were excluded. Additional use of intramuscular or IA (other joint) corticosteroid, or step-up therapy with oral steroids (prednisolone ≥ 7.5 mg/day) was not allowed for four weeks. No local or diluted anesthetic was added to the corticosteroid agent. Patients received a single infiltration with MA or TA (80 mg, 2 mL for both). Follow-ups were at 4, 12, and 24 weeks or whenever relapse (pain or swelling return to a condition similar to or greater than the baseline visit for week ≥ 1) was suspected. Patients rated pain and swelling at the target joint using a numerical rating scale (NRS) ranging from 0 to 10. The primary end point was flare time at 24 weeks, while secondary outcomes were change in pain and swelling reported by the patient at 4, 12 and 24 weeks, range of motion at 24 weeks, and adverse events. There was no difference between the groups in relation to the number of patients who relapsed within 24 weeks (ARR=0%, 95CI 0.15-0.15, NNH=NS). The mean time to relapse was not significantly different between the MA and TA groups (20.8 [95CI 18.8-22.7] weeks and 20.9 [95CI 19.0-22.8] weeks, respectively: p=0.9, hazard ratio = 1.0 [95CI 0.4-2.5]). In both groups, there was a significant reduction in pain and swelling at all visits compared to baseline (p=0.001, for all comparisons). Nevertheless, there were no significant intergroup differences (MA vs. TA) at 4, 12 and 24 weeks (p>0.05 for all comparisons). In the ITT analysis, at 24 weeks, the results (mean ± SD) for pain and swelling (MA vs. TA) were 2.5 (2.3) vs. 3.4 (3.1), p=0.33, and 2.4 (2.8) vs. 2.9 (3.0), p=0.16, respectively. There was an improvement in the number of patients with normal knee flexion in both groups, but no difference between them in up to 24 weeks (NNT=NS). None of the patients had vasovagal syncope, hematoma, infection or hypopigmentation. Therefore, no significant differences in efficacy were found between knee infiltrations with MA and TA in patients with chronic inflammatory arthritis over a 24-week period.[8] (**B**)

Another RCT[9] randomized 30 adult patients, in either outpatient or inpatient setting, with rheumatoid arthritis showing classic presentation or according to the American Rheumatism Association criteria, and with both knees symmetrically affected by the disease, into three groups with a single infiltration of: MA (40 mg in 1 mL; n=10), TH (20 mg in 1 mL; n=10) and prednisolone t-butyl acetate (20 mg in 1 mL; n=10). Patients treated with IA or systemic steroids three months prior to the beginning of the study were excluded. Drug therapy remained constant throughout the study. Patients were followed up for six weeks and the outcomes evaluated were pain measured by visual analogue scale (VAS), duration of morning stiffness, grip strength, Ritchie articular index and thermographic index. The improvement in mean pain score was higher with TH than with MA at week 1 (p<0.05), but this difference was not significant at two weeks, suggesting a faster onset of action with TH compared with MA. Overall efficacy was similar, with no improvement in joint index, morning stiffness or grip strength using any of the corticosteroids compared to the baseline visit (p>0.5 for all comparisons) within six weeks.[9] (**B**)

Three RCTs assessed the use of MA in patients with osteoarthritis, comparing it to TH or TA.

The first triple blind ECR included 100 patients on an intention-to-treat analysis with knee OA, grade II and III Kellgren-Lawrence radiological classification, VAS for knee pain ≥ 40 mm (maximum 100 mm), age ≥ 40 years, and failure to control symptoms with prior or current analgesic drugs and/or NSAIDs. Patients with corticosteroid or hyaluronic acid infiltration in the six months prior to the beginning of the study, using anticoagulants, and those with BMI ≥ 35 kg/m² were excluded. Patients who were severely ill were also excluded, while adjustments were made for analgesia, NSAIDs and chondroprotective agents. No new pharmacological or non-pharmacological therapy for knee OA was allowed during the study. Patients were randomized into two groups (50 in each), and were treated with a single injection of: THA

(40 mg [2 mL, 20 mg/mL]) and MA (40 mg [1 mL, 40 mg/mL, plus 1 mL of lidocaine to yield equivalent injection volumes]). Follow-up time was 24 weeks, with visits at 4, 12, and 24 weeks. Patient's pain assessment on VAS (0-100 mm) at week 4 was considered the primary endpoint, while patient's pain assessment at weeks 12 and 24 was one of the secondary outcomes. The other secondary outcomes were: global assessment of the disease by the patient (VAS), global assessment of the disease by the physician (VAS), global evaluation of the disease by the patient (Likert scale), the OA WOMAC (Western Ontario and McMaster Universities Osteoarthritis) questionnaire, the Lequesne algofunctional index, the OMERACT-OARSI (Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International) criteria for significant improvement and adverse events; all were evaluated at weeks 4, 12, and 24. Both groups showed significant benefits for pain (VAS) in four weeks, which was maintained to a lesser extent in 24 weeks. There was also sustained improvement in measures related to the secondary outcomes, including the WOMAC score (a composite measure of activity-related pain, function, and stiffness). However, there was no significant difference (mean±SD) between MA (48.1±28.7) and TH (46.4±31.8) in pain assessment on VAS at week 4 (p=0.352), as well as at the 12- and 24-week follow-up visits. None of the secondary outcomes assessed at 4, 12, and 24 weeks showed a statistically significant difference between MA and TH (p>0.05 for all comparisons). There was one adverse event in the MA group (post-infiltration arthritis [pain, swelling, redness and joint effusion]) the day after the procedure, and none in the TH group. This study provided strong evidence that IA injections of TH and MA are equally effective in reducing pain and improving function in patients with knee OA who were unable to control symptoms with analgesics or NSAIDs.[10] (**B**)

Another RCT randomized 120 patients (55-75 years) with complaints of knee pain who met the American College of Rheumatology (ACR) clinical criteria for knee osteoarthritis with pain severity ≤ 5 on VAS (0-10 cm), and grade ≥ 2 on the radiological classification scale of Kellgren and Lawrence (moderate to severe disease [grade IV]). Patients who received intra-articular steroid in the last three months were excluded. This 12-week (30-patient in each group) placebo-controlled (IA saline [NaCl 0.09%, 1 mL]) study compared a single injection of three different corticosteroids (MA 40 mg [1 mL], TA 40 mg [1 mL] and betamethasone disodium phosphate 3 mg [1 mL]). The outcomes analyzed for up to 12 weeks were: visual analog scale pain (0-10 cm [VAS]), function according to the Lequesne index (LI) and adverse events. The three corticosteroids promoted symptomatic and functional improvement for up to 12 weeks; however, MA was more effective in relieving pain compared with the other agents (TA, betamethasone disodium phosphate and saline) until week 6; p<0.05 for all comparisons. There was no statistically significant difference between the MA and TA groups regarding the improvement in functional status (LI) up to 12 weeks (analysis at weeks 1, 3, 6 and 12). No local or systemic complications associated with infiltrations were observed.[11] (**B**)

A third RCT included 57 patients (mean age 62.5 years) with knee OA and joint effusion, who met the ACR criteria (clinical and radiographic) for knee OA presenting at least grade II radiographic OA changes according to the Kellgren-Lawrence classification system. Patients treated with infiltration in the last three months were excluded, as were those with severe OA (complete obliteration of joint space on the X-ray). Patients were randomized to receive a single IA injection of MA 40 mg, 1mL (n=28) or TH 20 mg, 1 mL (n=29). The follow-up time was 8 weeks (0, 3 and 8 week analysis) and the outcomes assessed were pain intensity on VAS (0-100 mm), functional status according to Lequesne's index (LI), and time for ascending and descending stairs (TADS) using handrails. There was a significant improvement in pain with IA injection of MA and TH compared to the baseline visit; however, TH was more effective than MA in pain reduction (VAS) at week 3 (32.9 mm, 95CI 23.4-42.4 mm vs. 13.7 mm, 95CI 2.8-24.8 mm, p<0.01). This suggests a faster onset of pain relief with TH compared to MA. Only MA maintained this significant benefit (pain reduction) at week 8 compared to the baseline visit (p<0.05), but there was no difference between TH and MA at this follow-up (p=0.17). Compared with the baseline, both IA corticosteroids significantly improved the Lequesne index (LI) at week 3, but only MA maintained a significant benefit at week 8 (p<0.05). However, there was no significant difference between the two drugs in the assessment of function (LI and TADS) at 3 and 8 weeks (p>0.05 for all comparisons).[12] (**B**)

Discussion

Small number of good quality RCTs evaluating the efficacy of intra-articular infiltration of corticosteroids in rheumatoid arthritis or knee osteoarthritis, small sample in most studies, variable methodological quality, heterogeneity of outcome measures, different and short follow-up times, and doses of corticosteroids are factors that make it difficult to establish firm conclusions to guide treatment.

Recommendation

- MA and TA are equally effective in knee infiltration for the treatment of rheumatoid arthritis. (GRADE 1A)
- Infiltration with MA is more effective in relieving pain than TA in patients with knee OA in a maximum of six weeks, and equally effective in the improvement of function in up to 12 weeks. (GRADE 1B)
- The use of TH may be favored over MA for knee arthritis (RA or OA; 1 and 3 week analysis, respectively) based on the fastest onset of action for pain relief. (GRADE 1B)
- There is no difference between infiltration with MA and TH in pain relief for knee RA between 2 and 6 weeks. (GRADE 1B)
- There is no difference between infiltration with MA and TH in pain relief for knee OA between 4 and 24 weeks. (GRADE 1A)
- There is no difference between knee infiltration with MA and TH when functional improvement is evaluated, up to 6 weeks, in patients with RA. (GRADE 1B)
- There is no difference between knee infiltration with MA and TH when functional improvement is evaluated, up to 24 weeks, in patients with OA. (GRADE 1A)

GRADE 1A: strong recommendation, high-quality evidence; GRADE 1B: strong recommendation, moderate--quality evidence.

Conflict of interest

The authors declare no conflict of interest.

References

1. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. Cochrane Database Syst Rev. 2006; (2):CD005328. Review. Update in: Cochrane Database Syst Rev. 2015; (10):CD005328.
2. Gaujoux-Viala C, Dougados M, Gossec L. Efficacy and safety of steroid injections for shoulder and elbow tendonitis: a meta-analysis of randomised controlled trials. Ann Rheum Dis. 2009; 68(12):1843-9.
3. Centeno LM, Moore ME. Preferred intraarticular corticosteroids and associated practice: a survey of members of the American College of Rheumatology. Arthritis Care Res. 1994; 7(3):151-5.
4. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al.; National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum. 2008; 58(1):26-35.
5. Loeser RF. Age-related changes in the musculoskeletal system and the development of osteoarthritis. Clin Geriatr Med. 2010; 26(3):371-86.
6. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Clin Geriatr Med. 2010; 26(3):355-69.
7. Hajialilo M, Ghorbanihaghjo A, Valaee L, Kolahi S, Rashtchizadeh N, Amirkhiz MB, et al. A double-blind randomized comparative study of triamcinolone hexacetonide and dexamethasone intra-articular injection for the treatment of knee joint arthritis in rheumatoid arthritis. Clin Rheumatol. 2016; 35(12):2887-91.
8. Kumar A, Dhir V, Sharma S, Sharma A, Singh S. Efficacy of methylprednisolone acetate versus triamcinolone acetonide intra-articular knee injection in patients with chronic inflammatory arthritis: a 24-week randomized controlled trial. Clin Ther. 2017; 39(1):150-8.
9. Bird HA, Ring EF, Bacon PA. A thermographic and clinical comparison of three intra-articular steroid preparations in rheumatoid arthritis. Ann Rheum Dis. 1979; 38(1):36-9.
10. Lomonte AB, de Morais MG, de Carvalho LO, Zerbini CA. Efficacy of triamcinolone hexacetonide versus methylprednisolone acetate intraarticular injections in knee osteoarthritis: a randomized, double-blinded, 24-week study. J Rheumatol. 2015; 42(9):1677-84.
11. Yavuz U, Sökücü S, Albayrak A, Oztürk K. Efficacy comparisons of the intraarticular steroidal agents in the patients with knee osteoarthritis. Rheumatol Int. 2012; 32(11):3391-6.
12. Pyne D, Ioannou Y, Mootoo R, Bhanji A. Intra-articular steroids in knee osteoarthritis: a comparative study of triamcinolone hexacetonide and methylprednisolone acetate. Clin Rheumatol. 2004; 23(2):116-20.
13. Oxford Centre for Evidence-based Medicine – Levels of Evidence. Available from: http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/.
14. Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, Phillips B, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American college of chest physicians task force. Chest. 2006; 129(1):174-81.

Annex I

Structured question

- **P** – Adult patients with inflammatory arthritis or knee osteoarthritis.
- **I** – Single infiltration with methylprednisolone acetate injection.
- **C** – Triamcinolone acetonide or triamcinolone hexacetonide.
- **O** – Pain, function and adverse events.

Search strategy

Searches performed until June 18, 2017.

PubMed-Medline

- #1: (Methylprednisolone AND Triamcinolone) AND Injections, Intra-Articular = 54 studies retrieved.
- #2: (Methylprednisolone OR Triamcinolone OR Glucocorticoid) AND Injections, Intra-Articular AND (Shoulder Joint OR Shoulder OR Knee Joint OR Knee) = 637 studies retrieved.
- #3: 1 OR 2 = 669 studies retrieved.
- #4: (1 OR 2) AND Random* = 228 studies retrieved.

Central (Cochrane), Lilacs (via BVS)

- 'Methylprednisolone AND Triamcinolone'.

Manual search

- Reference within references, systematic reviews.

Articles retrieved

Obtaining evidence to be used for efficacy and harm analysis using methylprednisolone acetate, triamcinolone acetonide and triamcinolone hexacetonide in the treat-

ment of inflammatory arthritis and knee osteoarthritis included the following steps: clinical question elaboration, question structuring, search for evidence, critical evaluation, and selection of evidence.

Initially selected by the title, then by the abstract, and finally by its full text, the latter being subject to critical evaluation and extraction of results related to the outcomes.

Medline

- Selected based on title: 20.
- Selected based on abstract: 6.
- Selected after full text reading and critical assessment: 5.

Central (Cochrane)

- One study selected (excluded for lack of full text).

Lilacs (via BVS)

- Selected: 0.

Manual search – Reference within references, revisions and guidelines

- Selected: 0.

Exclusion criteria for selected studies

The strength of the evidence from experimental studies was defined taking into account the study design and corresponding bias risks, the results of the analysis (magnitude and precision), relevance and applicability (Oxford/GRADE).[13,14]

Language

Articles in languages other than Portuguese, English or Spanish.

According to publication

Only full-text studies were considered for critical assessment.

Data extraction

The results obtained from the included studies were related to means and standard deviations of the scores (pain, function), and to the number of patients who presented recurrence (flare) with IA therapy, comparing methylprednisolone acetate with triamcinolone acetonide or triamcinolone hexacetonide, in the treatment of inflammatory arthritis and osteoarthritis of the knee. When expressed graphically, whenever possible, the results were estimated from their respective figures.

In Annex I, Tables 1 to 15, the characteristics of the study, including results and bias, are described.

Critical evaluation and strength of evidence

The recommendations were elaborated based on the authors' discussion about the selected literature, following the Oxford Grades of Recommendation.[13]

Data analysis and expression

We were not able to group studies, but the outcomes used the same measures to express their individual results. All results are available in the attached tables.

TABLE 1 Descriptive table of study characteristics.

Study	Population (N)	Intervention (N)	Comparison (N)	Outcome	Follow-up time
Kumar et al.[8]	A total of 170 patients (18 to 65 years) with rheumatoid arthritis (n=89) or spondyloarthrosis (n=11) and a severely swollen knee joint (defined as duration ≥ 1 weeks and < 24 weeks) were included Patients who received steroid infiltration in the same joint in the last 3 months were excluded	N=50 Intra-articular injection of MA (80 mg, 2 mL) at the knee joint No local anesthetic was injected into the skin or mixed with steroids Additional use of intramuscular or IA (other joint) corticosteroid, or step-up therapy with oral steroids (prednisolone ≥7.5 mg/day) was not allowed for 4 weeks	N=50 Intra-articular injection of TA (80 mg, 2 mL) at the knee joint	The primary outcome was time to relapse at 24 weeks Secondary outcomes included changes in pain reported by the patient and swelling at 4, 12 and 24 weeks; range of motion (normal, mild, moderate or severely restricted) at 24 weeks and adverse events Patients rated pain and swelling at the target joint using a numerical rating scale (NRS) ranging from 0 to 10	4, 12 and 24 weeks or whenever relapse was suspected

MA: methylprednisolone acetate; TA: triamcinolone acetonide; NRS: numerical rating scale.

TABLE 2 Descriptive table of biases in the randomized clinical trial (Kumar et al.[8])

Question focal?	Proper randomization?	Blinded allocation?	Blinding?	Losses described? < 20%?	Prognostic characteristics similar between groups?	Appropriate outcomes? Appropriately measured? Timely?	ITT analysis
Yes	Yes	Yes	Patient blinding	Described and < 20%	Yes	Yes	Yes

ITT: intention-to-treat analysis.
Sample calculation: present.

TABLE 3 Outcomes and results of Kumar et al.

Study	Outcome	Results
Kumar et al.[8]	Primary outcome: time to relapse in 24 weeks	Nine patients relapsed in each group over 24 weeks (ARR=0%, 95CI 0.15-0.15, NNH=NS). The mean time to relapse was not significantly different between the MA and TA groups (20.8 [95CI 18.8-22.7] weeks and 20.9 [95CI 19.0-22.8] weeks, respectively: p=0.9, hazard ratio = 1.0 [95CI 0.4-2.5])
Rheumatoid arthritis and spondyloarthritis	Secondary outcomes (4, 12 and 24 weeks):	
	Change reported by the patient (NRS) • pain • swelling	In both groups, there was a significant reduction in pain and swelling at all visits compared to the baseline visit (p=0.001). However, there were no significant intergroup (MA vs. TA) differences (4, 12 and 24 weeks). In the ITT analysis, at 24 weeks, the results for pain and swelling (MA vs. TA) were 2.5 (2.3) vs. 3.4 (3.1), p=0.33, and 2.4 (2.8) vs. 2.9 (3.0), p=0.16, respectively
	Range of movement in 24 weeks	There were no significant intergroup differences in range of motion within 24 weeks. The normal flexion of the knee joint was present in 28 and 25 patients (p=0.17) at baseline, and in 38 and 37 patients at 24 weeks (NNT=NS)
	Adverse events	None of the patients had infection, hematoma or hypopigmentation

* mean and SD.
CI: confidence interval; MA: methylprednisolone acetate; TA: triamcinolone acetonide; NRS: numerical rating scale; NNH: number needed to harm; NS: non significant; NNT: number needed to treat.

TABLE 4 Descriptive table of study characteristics.

Study	Population (N)	Intervention (N)	Comparison (N)	Outcome	Follow-up time
Bird et al.[9]	Thirty patients in an outpatient or inpatient setting presenting classic or defined (ARA criteria) rheumatoid arthritis, with both knees symmetrically affected by the disease Patients who received intra-articular or systemic steroids in the previous 3 months were excluded Drug therapy remained constant throughout the study	N=10 Single injection in one knee with MA (40 mg in 1 mL)	N=10 Single injection in one knee with TH (20 mg in 1 mL) N=10 prednisolone t-butyl acetate (20 mg in 1 mL) (comparison not included in this review)	Pain on VAS Duration of morning stiffness Grip strength Ritchie articular index Thermographic index	6 weeks

ARA: American Rheumatism Association; MA: methylprednisolone acetate; TH: triamcinolone hexacetonide; VAS: visual analogue scale.

TABLE 5 Descriptive table of biases in the randomized clinical trial (Bird et al.[9]).

Question focal?	Proper randomization?	Blinded allocation?	Blinding?	Losses described? < 20% ?	Prognostic characteristics similar between groups?	Appropriate outcomes? Appropriately measured? Timely?	ITT analysis
Yes	Not described	Not described	Double blinded Not described	Does not describe losses	Yes	Outcomes are appropriate; however, values for pain (VAS) and range of motion (ROM) were not reported	No reference

ITT: intention-to-treat analysis.
Sample calculation: present.

TABLE 6 Outcomes and results of Bird et al.

Study	Outcome	Results
Bird et al.[9]	Follow-up 6 weeks	Improvement of pain: TH > MA at 1 week ($p<0.05$), difference not maintained at 2 weeks ($p>0.1$)
Rheumatoid arthritis	• Pain on VAS • Duration of morning stiffness • Grip strength • Ritchie articular index	Compared with the baseline • Morning stiffness did not show significant improvement in any group, $p>0.5$ • Grip strength did not show significant changes in any group, $p>0.5$ • Joint index did not show significant improvement in any group, $p>0.5$ The differences between MA and TH groups were not significant for these outcomes (duration of morning stiffness, grip strength, Ritchie's Articular index) at any follow-up, up to 6 weeks

MA: methylprednisolone acetate; TH: triamcinolone hexacetonide; VAS: visual analogue scale.

TABLE 7 Descriptive table of study characteristics.

Study	Population (N)	Intervention (N)	Comparison (N)	Outcome	Follow--up time
Lomonte et al.[10]	100 patients analyzed according to ITT Patients with knee OA, Kellgren-Lawrence grade II and III radiologic classification, knee pain on VAS ≥ 40 mm (maximum 100 mm), age ≥ 40 years and failure to control symptoms with previous or current analgesics and/or NSAIDs The following were excluded: patients with severe disease; infiltration of corticosteroid or hyaluronic acid in the previous 6 months; use of anticoagulants	N=50 Single intra-articular injection of MA 40 mg in the most symptomatic knee No new pharmacological or non-pharmacological therapy for knee OA was allowed during the study	N=50 Single intra-articular injection of TH 40 mg in the most symptomatic knee	Primary outcome: Patient pain assessment on VAS (0-100 mm) at week 4 Secondary outcomes: • Patient pain assessment at weeks 12 and 24. • Global disease assessment performed by the patient (VAS) at weeks 4, 12 and 24. • Global disease assessment performed by the physician (VAS) at weeks 4, 12 and 24. • Global disease assessment performed by the patient (Likert scale) at weeks 4, 12 and 24. • OA WOMAC (pain, function and activityrelated stiffness) questionnaire at 4,12 and 24 weeks • Lequesne algofunctional index at weeks 4,12 and 24 • OMERACT-OARSI criteria at weeks 4, 12 and 24 • Adverse events	Assessment at weeks 4, 12 and 24

OA: osteoarthritis; MA: methylprednisolone acetate; TH: triamcinolone hexacetonide; NSAIDs: non-steroidal anti-inflammatory drugs; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities; OMERACT-OARSI: Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International.

TABLE 8 Descriptive table of biases in the randomized clinical trial (Lomonte, et al.[10]).

Question focal?	Proper randomization?	Blinded allocation?	Blinding?	Losses described? < 20% ?	Prognostic characteristics similar between groups?	Appropriate outcomes? Appropriately measured? Timely?	ITT analysis
Yes	Yes	Yes	Triple-blinded (patient, intervention and evaluator)	Yes and < 20% (loss=10%)	Yes	Yes	Yes

ITT: intention-to-treat analysis.
Sample calculation: present.

TABLE 9 Outcomes and results of Lomonte et al.

Study	Outcome	Results
Lomonte et al.	Pain on visual analogue scale (VAS, 0-100 mm) at weeks 4, 12 and 24	There was no significant difference between MA (48.1±28.7)* and TH (46.4±31.8)* in pain assessment on VAS at week 4 (p=0.352), as well as at the 12- and 24-week follow-up visits
Osteoarthritis		At follow-up, week 4, 12 and 24:
	Global disease assessment performed by the patient (VAS and Likert scale [LS])	There was no difference between the groups during the study (p=0.94 on VAS and p=0.86 on [LS])
		There was no difference between the groups during the study (p=0.54)
	Global disease assessment performed by the physician (VAS).	There was no significant difference between treatments in the total WOMAC questionnaire score during the study (p=0.23)
	WOMAC questionnaire	The improvement in LI was similar between the MA and TH groups (p=0.69)
	Lequesne index (LI)	There was no significant difference between MA and HT in terms of response to treatment according to the OMERACT-OARSI criteria (p=0.54)
	OMERACT-OARSI criteria	
	Adverse events	1 adverse event in the MA group – post-infiltration arthritis (pain, swelling, redness and joint effusion) on the day following the procedure and none in the TH group

* mean ±SD
OA: osteoarthritis; MA: methylprednisolone acetate; TH: triamcinolone hexacetonide; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities; OMERACT-OARSI: Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International.; LI: Lequesne index.

TABLE 10 Descriptive table of characteristics of the randomized clinical trial (Yavuz et al.[11]).

Study	Population (N)	Intervention (N)	Comparison (N)	Outcome	Follow-up time
Yavuz et al.[11]	N=120 Patients with complaints of knee pain who met the American College of Rheumatology (ACR) clinical criteria for knee osteoarthritis with pain severity ≤ 5 on VAS (0-10 cm), and grade ≥ 2 on the radiological classification scale of Kellgren and Lawrence (moderate to severe disease). Patients who received intra-articular steroid in the last 3 months were excluded	N=30 Single intra-articular injection of MA 40 mg (1 mL)	N=30 Single intra-articular injection of TA 40 mg (1 mL) N=30 IA disodium phosphate betamethasone (Group 3) N=30 IA saline (placebo – Group 4)	Pain on visual analogue scale (0-10 cm [VAS]) Function according to Lequesne index (LFI) Adverse events	Weeks 1, 3, 6 and 12

IA: intra-articular; LFI: Lequesne Functional Index.

TABLE 11 Descriptive table of biases in the randomized clinical trial (Yavuz et al.[11]).

Question focal?	Proper randomization?	Blinded allocation?	Blinding?	Losses described? < 20%?	Prognostic characteristics similar between groups?	Appropriate outcomes? Appropriately measured? Timely?	ITT analysis
Yes	Strategy was not reported	Not described	Strategy was not reported	Not described	Yes	Yes	Not reported

ITT: intention-to-treat analysis.
Sample calculation: absent.

TABLE 12 Outcomes and results of Yavuz et al.

Study	Outcome	Results
Yavuz et al.[11]	Analyses at weeks 1, 3, 6 and 12	The three corticosteroids promoted symptomatic and functional improvement for up to 12 weeks; however, MA was more effective in relieving pain compared with the other agents (TA,
Osteoarthritis	Pain on visual analogue scale (0-10 cm [VAS])	betamethasone disodium phosphate and saline) until week 6; p<0.05 for all comparisons
	Lequesne Functional Index (LI)	There was no statistically significant difference between the MA and TA groups regarding improvement in functional status (LI) up to 12 weeks
	Adverse events	No local or systemic complications associated with infiltrations were observed

MA: methylprednisolone acetate; TA: triamcinolone acetonide; VAS: visual analogue scale.

TABLE 13 Descriptive table of study characteristics.

Study	Population (N)	Intervention (N)	Comparison (N)	Outcome	Follow-up time
Pyne et al.[12]	Patients with knee OA and joint effusion, who met the ACR criteria (clinical and radiographic) for knee OA presenting at least grade II radiographic OA changes according to the Kellgren-Lawrence classification system. Patients treated with infiltration in the last 3 months were excluded, as were those with severe OA	N=28 IA injection of MA 40 mg (1 mL)	N=29 IA injection of TH 20 mg (1 mL)	Pain severity according to VAS (0-100 mm) Lequesne Functional Index (LI) Time to ascend and descend stairs using handrails (TADS)	Weeks 0, 3 and 8

ACR: American College of Rheumatology; MA: methylprednisolone acetate; TH: triamcinolone hexacetonide; VAS: visual analogue scale.

TABLE 14 Descriptive table of biases in the randomized clinical trial (Pyne et al.).

Question focal?	Proper randomization?	Blinded allocation?	Blinding?	Losses described? < 20%?	Prognostic characteristics similar between groups?	Appropriate outcomes? Appropriately measured? Timely?	ITT analysis
Yes	Strategy was not reported	Strategy was not reported	Double-blinded (patient and evaluator)	Not described	Yes	Yes	No

ITT: intention-to-treat analysis.
Sample calculation: present.

TABLE 15 Outcomes and results of Pyne at al.

Study	Outcome	Results
Pyne et al.[12]	Follow-up 3 to 8 weeks	TH was more effective than MA in reducing pain at week 3 (32.9 mm, 95CI 23.4-42.4 mm vs. 13.7 mm, 95CI 2.8-24.8 mm, p <0.01); this difference was lost at week 8 (p=0.17)
Osteoarthritis	Pain severity according to VAS (0-100 mm) • Lequesne Functional Index (LI) • Time to ascend and descend stairs using handrails (TADS)	There was no significant difference between the two drugs (MA vs. TH) in the assessment of function (LI and TADS) at 3 and 8 weeks (p>0.05 for all comparisons)

LI: Lequesne index.

Description of evidence

The available evidence will follow some principles to be displayed:

- by outcome;
- by study design (randomized clinical trial).

Recommendation

The global synthesis will be elaborated considering the described evidence and the strength (Oxford/GRADE)[13,14] will be estimated as 1b and 1c (grade A) or strong, and 2a, 2b and 2c (grade B) or moderate, weak or very weak. The strongest evidence will be considered.