Efficacy of Triamcinolone Hexacetonide versus Methylprednisolone Acetate Intraarticular Injections in Knee Osteoarthritis: A Randomized, Double-blinded, 24-week Study

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ABSTRACT. *Objective.* Intraarticular (IA) corticosteroid injections are broadly used in knee osteoarthritis (OA); however, the best corticosteroid agent is not well defined. The aim of the present study was to compare the efficacy of triamcinolone hexacetonide (TH) and methylprednisolone acetate (MA) injections in knee OA.

Methods. Patients with symptomatic knee OA and Kellgren-Lawrence grade II or III were randomized to receive 40 mg of IA TH or MA. Evaluations were performed at 4, 12, and 24 weeks. The primary outcome was a change in the patient's assessment of pain by visual analog scale from baseline to Week 4. Secondary outcomes included a global assessment of the disease by patients and physicians, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Lequesne index (LI), and Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International (OMERACT-OARSI) criteria of response. Generalized estimating equations were used in statistical analysis.

Results. The intention-to-treat population included 100 patients; 50 in each study arm. A significant improvement in pain was observed at Week 4 for both groups (p < 0.0001), with no difference between them (p = 0.352). This improvement was sustained up to Week 24. A significant improvement from the baseline was observed for both the patient's and the physician's global assessments, WOMAC questionnaire, and LI, with no differences between the groups. Improvements in the secondary outcomes were sustained during the study. The OMERACT-OARSI criteria of response was achieved by 74% and 72% of patients in the TH and the MA groups, respectively.

Conclusion. Both IA therapies are equally effective, and improvement in pain and function can be sustained for up to 24 weeks. Controlled-trials.com identifier: ISRCTN15077843. (J Rheumatol First Release July 1 2015; doi:10.3899/jrheum.150297)

Key Indexing Terms:
KNEE OSTEOARTHRITIS   INTRAARTICULAR INJECTIONS
ADRENAL CORTEX HORMONES   TRIAMCINOLONE HEXACETONIDE
METHYLPREDNISOLONE ACETATE   QUESTIONNAIRES

Osteoarthritis (OA) is the most common chronic joint disease in the world[1]. Symptomatic knee OA occurs in about 6% of adults aged 30 years or older[2] and its prevalence increases with aging[3]. Significant morbidity results from this condition, leading to pain and disability in over 3.6% of the global population, and posing knee OA management as a significant healthcare challenge[4].

The main goals of the symptomatic treatment of knee OA are to promote pain relief and functional improvement[5]. In this regard, analgesics and nonsteroidal antiinflammatory drugs (NSAID) may fail to achieve a clinical response, and intraarticular (IA) corticosteroid injections can be considered. In fact, there is a large body of evidence on the effectiveness of IA corticosteroid injections, particularly in the short term[6].

A large survey in the United States revealed that more than 95% of rheumatologists use IA corticosteroid injections in knee OA treatment[7], but there is still controversy in choosing the most effective steroid preparation. IA triamcinolone hexacetonide (TH) and methylprednisolone acetate (MA) are the most commonly used and studied preparations[8,9], but only

1 trial compared both agents and revealed that TH was more effective at Week 3, while MA was better at Week 8. Those findings preclude a conclusive definition about choosing one or the other[10].

Considering the health burden of knee OA and the broad use of IA corticosteroid injections, our present study aimed to compare the efficacy of IA TH and IA MA in patients with defined knee OA.

MATERIALS AND METHODS

Study design. This was a double-blind, randomized, parallel-group study to compare IA TH with IA MA for the treatment of knee OA. Patients were evaluated on weeks 4, 12, and 24 after IA injection by a blinded assessor.

Our study was approved by the local ethics committee and conducted in accordance with the amended Declaration of Helsinki and adhered to the Good Clinical Practice International Conference on Harmonisation Tripartite Guideline. All patients gave written informed consent before any trial procedure.

This clinical trial was registered in www.controlled-trials.com/ISRCTN15077843, and this manuscript followed the Consolidated Standards of Reporting Trials statement.

Eligibility criteria. Patients were recruited from the outpatient clinic of the Department of Rheumatology of Hospital Heliópolis, localized in the state of São Paulo, Brazil. To be eligible to participate, patients had to fulfill the following inclusion criteria: diagnosis of knee OA according to the American College of Rheumatology criteria[11], Kellgren-Lawrence (KL) radiographic grade II (definite osteophytes, unimpaired joint space) or grade III (moderate multiple osteophytes, definite narrowing of joint space, some sclerosis, and possible deformity of bone contour) of the knee[12], visual analog scale (VAS) for knee pain of at least 40 mm (maximum 100 mm), age ≥ 40 years, and failure to control OA symptoms with previous or current analgesics and/or NSAID. Exclusion criteria were any other rheumatic or inflammatory condition, symptomatic disease of the lower limbs (other than knee OA), serious and/or uncontrolled concomitant medical illness, body mass index ≥ 35 kg/m^2, IA injection of corticosteroid or hyaluronic acid in the previous 6 months, knee replacement in the targeted joint, local or systemic infection, pregnancy, skin lesions in the IA injection site, current physical therapy for the knee, known hypersensitivity to corticosteroids or lidocaine, and the use of anticoagulants.

Intervention. Consecutive patients fulfilling eligibility criteria were randomized 1:1 to receive a single-joint injection in the most symptomatic knee of TH 40 mg (Apsen Farmacêutica S/A) or MA 40 mg (União Química Farmacêutica Nacional S/A) at the baseline visit. The allocation of patients to one of the study groups was determined by a computer-generated randomization list. Concealed randomization was done by opaque sealed envelopes that were available only to an independent assessor. The independent assessor prepared the injection, but did not perform the procedure; neither did he apply questionnaires to the patients.

An independent rheumatologist with 10 years' experience, who had administered over 1000 joint injections, was blinded for all other study procedures and performed all the knee injections. The aseptic technique was used. For local anesthesia, the skin and subcutaneous tissue were infiltrated down to the capsule with 2% lidocaine without epinephrine. For joint injections, 22 gauge 1 1/4″ (0.7 × 30 mm) needles were used. Because the available TH preparation had a different concentration from MA (20 mg/ml vs 40 mg/ml, respectively), patients in the TH group received a total volume of 2 ml of TH. Patients in the MA group received a total volume of 2 ml consisting of 1 ml of MA and 1 ml of lidocaine. In order to keep the blindness, adhesive tapes were applied to the syringes so both patients and physicians could not see the aspect of the injected corticosteroid. All knee injections were performed by medial midpatellar approach. Joint aspiration was attempted for all subjects and the presence or absence of effusion was reported. Joint fluids were sent for laboratory analysis.

Clinical evaluations. Demographic and clinical data were collected at the baseline visit and included sex, age, disease duration, height, weight, the most symptomatic knee, and KL radiographic evaluation. Current use was reported for analgesics, NSAID, chondroprotective agents, and opioids. These drugs had to remain stable during the study. No new pharmacological or nonpharmacological therapies for knee OA were allowed during the study.

Patients were instructed to report evaluations considering only the injected knee.

The following outcome measures were applied:

(1) Primary outcome:
• Patient's assessment of pain in the targeted knee by VAS ranging from 0 (no pain) to 100 mm (unbearable pain) at Week 4[13]. The question was: "In this line, where do you grade your pain today?"

(2) Secondary outcomes:
• Patient's assessment of pain by VAS at weeks 12 and 24.
• Patient's global assessment (PtGA) and physician's global assessment (PGA) of disease by VAS.
• PtGA of disease by Likert scale (LS) with the following categories: (1) very well — no symptom and no limitation of normal daily living activities, (2) well — mild symptoms and no limitation of normal daily living activities, (3) fair — moderate symptoms and limitation of some daily living activities, (4) bad — severe symptoms and incapacity to perform most daily living activities, and (5) very bad — very severe symptoms that are unbearable and incapacity to perform all daily living activities.
• Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire with overall score ranging from 0 to 96 points (higher scores are representative of worse function)[14]. The pain, stiffness, and function subsections were not evaluated separately.
• Lequesne index (LI) with overall score ranging from 0 to 24 points. LI was categorized as follows: mild (1–4 points), moderate (5–7 points), severe (8–10 points), very severe (11–13 points), and extremely severe (≥ 14 points)[15].
• Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International (OMERACT-OARSI) response criteria defined by improvements from the baseline in patient's assessment of pain (VAS) or in WOMAC physical function subscore ≥ 50% with absolute changes ≥ 20 mm, or an improvement ≥ 20% with absolute changes ≥ 10 mm in at least 2 of the following 3 measures: the patient's assessment of pain (VAS), the WOMAC physical function subscore, and the PtGA of disease[16,17].

Safety evaluations were performed after the IA injections throughout Week 24, with special attention to pain, swelling, redness, and effusion. Adverse events were recorded.

Recruiting started in December 2010 and the last evaluation was performed in May 2013. Screening and randomization were done on the same day for each patient.

Statistical analysis. The sample size calculation of 100 patients was determined by a 2-sided Student t test with a 5% significance level, 90% power, 1:1 randomization allocation, 20 mm detectable difference between treatments in VAS patients' pain assessment change from baseline at Week 4, and SD of 27 mm[10], allowing a 20% dropout rate per group.

Efficacy analyses were performed in the intention-to-treat (ITT) population, defined as all randomized patients who received treatment with at least 1 postinjection visit. Change from the baseline in VAS patients' pain was used in the primary analysis, using a generalized linear model for repeated measures, normal distribution, identity link function, and fixed factors week, treatment, and interaction between week and treatment. Generalized estimating equation (GEE) analyses were performed with Wald statistics for Type 3 contrasts[18]. Treatment profiles were compared when interaction was deemed to be not significant. The difference between the 2 groups in the model-estimated change from the baseline at Week 4 was the primary endpoint analysis. Secondary continuous efficacy outcome measures were analyzed with the same model as the primary one. Binary and categorical outcomes were also analyzed with the GEE regression model; the first with binomial distribution and logit link, and the last with multi-

nomial distribution and cumulative logit link function. Wald statistics for Type 3 contrasts were used for comparisons between visits. Tukey-Kramer multiple comparison adjustment was used. The week effect that represents the response to the treatment over weeks for each outcome measure was analyzed by the GEE method.

The SAS 9.3 system was used for statistical analyses. p value < 0.05 was considered significant.

RESULTS

A total of 106 patients were randomized in our study. Six patients did not provide any efficacy data since they did not return to any study visit after the intervention. They were not included in the efficacy analysis. There were 100 patients included in the ITT population; 50 in each study group. One patient in the MA group and 3 in the TH group had only a visit Week 4 evaluation while 1 patient in the TH group had only visits weeks 4 and 12 assessments. There were 46 patients in the TH group and 49 in the MA group who completed our study (Figure 1).

Baseline demographic and clinical characteristics were comparable between treatment groups (Table 1). Most patients were elderly women who were overweight with long-lasting disease and KL radiographic grade III. Joint

effusion detected by arthrocentesis was present in 18 patients in the MA group and in 19 patients in the TH group, with a total of 37% of the studied population. No crystals were found in the joint fluid analyses. Concomitant medications remained stable during the study and NSAID were the most commonly used.

Primary outcome. There was no significant difference between the TH and MA groups in the assessment of pain by VAS at Week 4 (p = 0.352). Improvement in pain from baseline was observed in both groups at Week 4 (p < 0.001) and sustained in the following 20 weeks with no statistical difference between Week 4, Week 12, and Week 24 evaluations (p = 0.272 for both groups; Table 2). There was no difference between the groups at any study visit (Figure 2).

Secondary outcomes. There were no significant differences between the TH and MA groups in PtGA and PGA of disease by VAS at any study visit (p = 0.94 and p = 0.54, respectively; Figures 3A and 3B). An improvement from baseline in PtGA and PGA was observed for both groups during the study. However, a statistically significant difference in PtGA of disease was observed for both treatments from Week 4 to
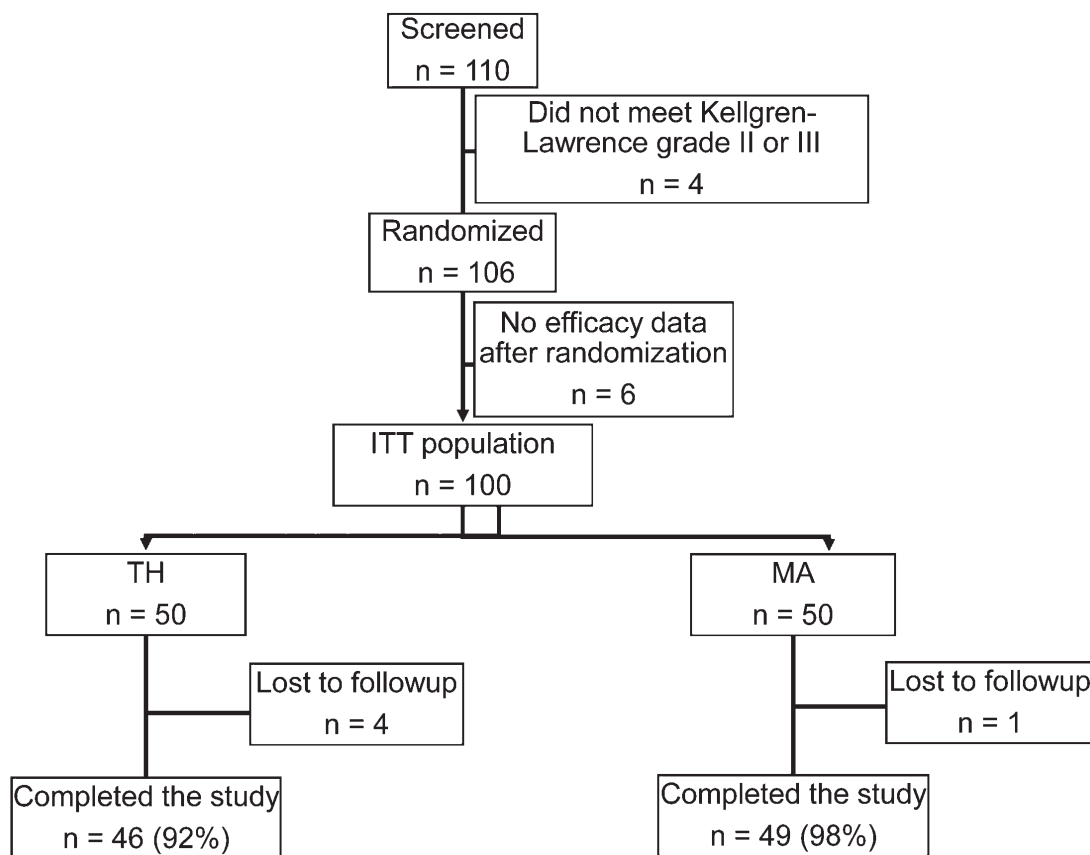

Figure 1. Flowchart of patients' dispositions. ITT: intention-to-treat; TH: triamcinolone hexacetonide; MA: methylprednisolone acetate.

Table 1. Baseline demographic and clinical characteristics. Values are n (%) unless otherwise specified.

Characteristic	TH, n = 50	MA, n = 50	p
Female	49 (98)	45 (90)	0.204
Age, yrs, mean (SD)	64.8 (8.3)	66.2 (8.2)	0.387
Disease duration, yrs, mean (SD)	7.9 (6.0)	8.3 (7.4)	0.770
BMI, kg/m^2, mean (SD)	28.8 (2.7)	28.5 (2.8)	0.246
Kellgren-Lawrence grade			0.648
II	12 (24)	14 (28)	
III	38 (76)	36 (72)	
Joint effusion*	19 (38)	18 (36)	1.0
Concomitant analgesic use	22 (44)	16 (32)	0.303
Concomitant NSAID use	25 (50)	28 (56)	0.689
Concomitant opioid analgesic use	1 (2)	1 (2)	1.0
Concomitant chondroprotective agent use[†]	2 (4)	2 (4)	1.0
Patient's pain assessment, 0–100 mm VAS, mean (SD)	82.7 (18.7)	78.5 (19.5)	0.269
PtGA, 0–100 mm VAS, mean (SD)	83.1 (18.9)	75.8 (26.6)	0.115
PGA, 0–100 mm VAS, mean (SD)	74.4 (15.8)	72.1 (18.2)	0.493
PtGA, Likert scale			0.772
Very mild	0 (0)	0 (0)	
Mild	1 (2)	3 (6)	
Moderate	20 (40)	17 (34)	
Severe	25 (50)	25 (50)	
Very severe	4 (8)	5 (10)	
WOMAC, 0–96 points, points (SD)	53.1 (17.2)	49.8 (19.7)	0.371
Lequesne index			0.613
Mild	0 (0)	1 (2)	
Moderate	1 (2)	4 (8)	
Severe	4 (8)	3 (6)	
Very severe	22 (44)	20 (40)	
Extremely severe	23 (46)	22 (44)	

* Detected by arthrocentesis. [†] Glucosamine and chondroitin sulphate (2 MA), glucosamine sulphate (1 TH), and diacerein (1 TH). TH: triamcinolone hexacetonide; MA: methylprednisolone acetate; BMI: body mass index; NSAID: nonsteroidal antiinflammatory drug; VAS: visual analog scale; PtGA: patient's global assessment; PGA: physician's global assessment; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2. Summary of efficacy of TH and MA compared to baseline in the ITT population. Values are n or mean ± SD unless otherwise specified.

Outcome Measure	TH, n = 50					MA, n = 50				
	Baseline	Week 4	Week 12	Week 24	p[†]	Baseline	Week 4	Week 12	Week 24	p[†]
VAS, 0–100 mm*										
Patient's pain assessment	82.7 ± 18.7	46.4 ± 31.8*	51.6 ± 31.7*	54.1 ± 33.8*	0.272	78.5 ± 19.5	48.1 ± 28.7*	51.6 ± 28.4*	50.2 ± 30.9*	0.272
PtGA	83.1 ± 18.9	53.4 ± 33.1*	59.5 ± 33.1*	63.7 ± 30.5*	0.020	75.8 ± 26.6	49.9 ± 31.6*	49.2 ± 27.9*	56.8 ± 29.0*	0.013
PGA	74.4 ± 15.8	45.0 ± 27.4*	49.9 ± 26.9*	53.3 ± 27.2*	0.079	72.1 ± 18.2	48.6 ± 25.1*	48.9 ± 24.4*	52.2 ± 28.1*	0.079
PtGA by LS, %										
Very mild	0	8	2	0		0	2	6	4	
Mild	2	26	26	16		6	22	20	16	
Moderate	40	50	46	54		34	60	56	48	
Severe	50	16	24	26		50	14	12	26	
Very severe	8	0	2	4		10	2	6	6	
WOMAC, 0–96 points, points (SD)*	53.1 ± 17.2	33.1 ± 21.1*	35.8 ± 22.4*	35.5 ± 22.3*	0.028	49.8 ± 19.7	35.9 ± 22.7*	34.1 ± 20.3*	36.4 ± 22.9*	0.028
Lequesne index, %										
Mild	0	16	14	14		2	16	20	20	
Moderate	2	16	10	12		8	10	8	14	
Severe	14	20	28	20		18	26	32	16	
Very severe	38	32	28	24		28	18	18	24	
Extremely severe	46	16	20	30		44	30	22	26	
OMERACT-OARSI responders, %	—	74	62	64		—	72	72	70	—

* p < 0.001 versus baseline. [†] p value for comparison of results from Week 4 to Week 24 within group. TH: triamcinolone hexacetonide; MA: methylprednisolone acetate; ITT: intention to treat; VAS: visual analog scale; PtGA: patient's global assessment; PGA: physician's global assessment; LS: Likert scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; OMERACT-OARSI: Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International.
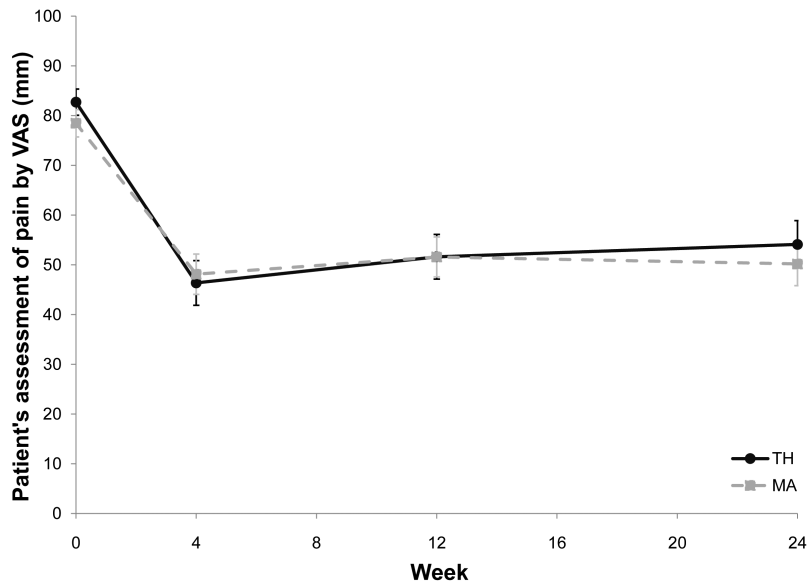
Figure 2. Mean patient's pain assessment by VAS over 24 weeks. (mean and SE plotted). p = 0.523 TH versus MA. VAS: visual analog scale; TH: triamcinolone hexacetonide; MA: methylprednisolone acetate; SE: standard error.
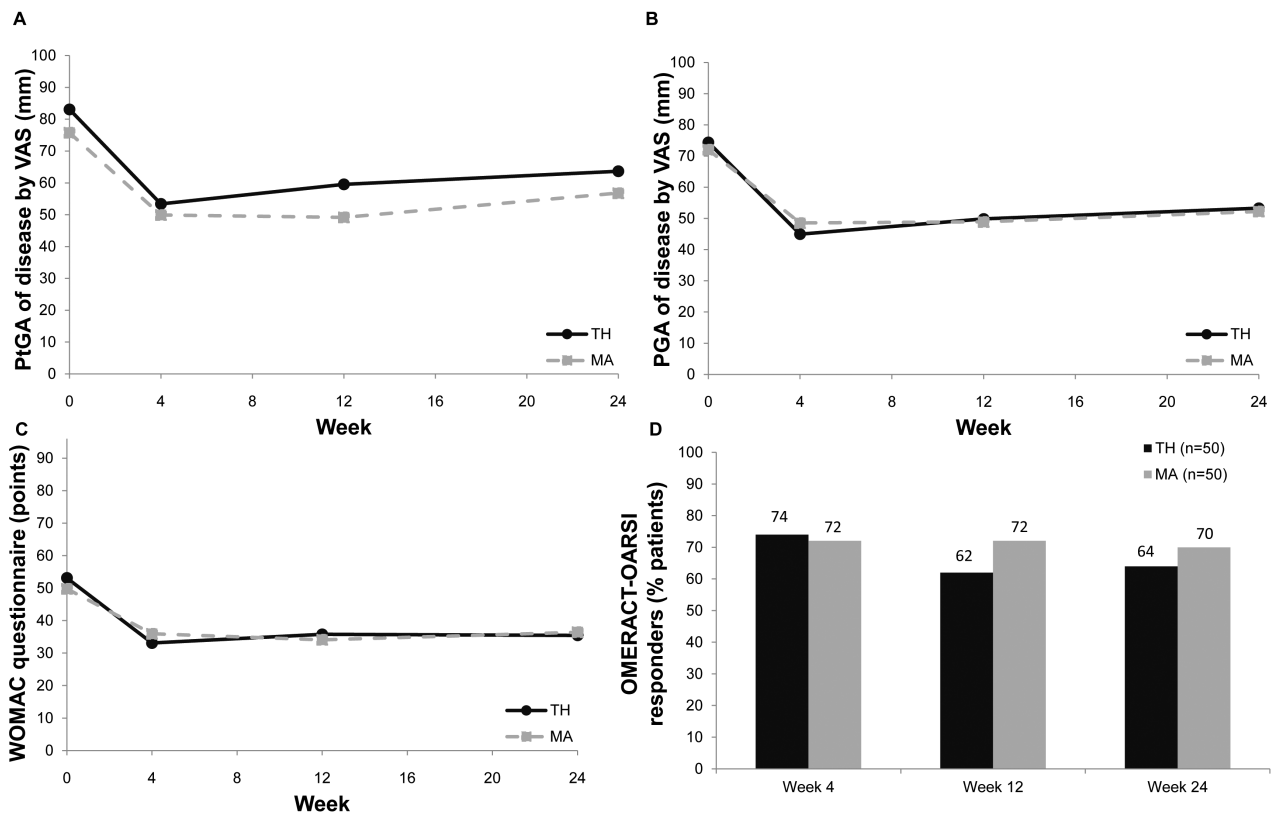

Figure 3. A. Mean PtGA of disease by VAS over 24 weeks. B. Mean PGA of disease by VAS over 24 weeks. C. Mean WOMAC questionnaire responses over 24 weeks. D. Percentage of patients achieving OMERACT-OARSI criteria of response at weeks 4, 12, and 24. p = not significant for all TH versus MA comparisons at individual timepoints. PtGA: patient's global assessment; VAS: visual analog scale; PGA: physician's global assessment; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; OMERACT-OARSI: Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International; TH: triamcinolone hexacetonide; MA: methylprednisolone acetate.

Week 24 (p = 0.020 for TH group, and p = 0.013 for MA group; Table 2). No significant differences along the weeks were observed in the PGA of disease (p = 0.079 for both groups; Table 2).

No differences between TH and MA groups were observed in PtGA of disease by LS (p = 0.86). There was a significant difference between baseline and Week 4 distributions for both groups (p less than 0.0001). At baseline, 50% of patients of each group had severe disease, while at Week 4, only 16% of patients of the TH group and 14% of patients of the MA group still had severe disease (Table 2). There was no significant difference between Week 4 and Week 12 evaluations by LS for both groups (p = 0.67). On the other hand, there was a statistically significant worsening of patients' evaluation by LS for both treatment groups at Week 24 in comparison to Week 12 (p = 0.02).

WOMAC questionnaire. There was no significant difference between treatments in the total WOMAC score during the study (p = 0.23; Figure 3C). At Week 4, both treatments resulted in a significant reduction in the WOMAC score in comparison to baseline (p < 0.0001; Table 2). This improvement was sustained in the following 20 weeks for both groups.

Differences in LI. Improvements in the LI were similar between the TH and MA groups during the study (p = 0.69). Both treatments led to a significant difference between baseline and Week 4 distributions (p < 0.0001). No significant differences were observed from Week 4 onward for both groups, showing a sustained response. At baseline, 46% of the patients in the TH group and 44% of patients in the MA group had extremely severe disease. At Week 4, this percentage dropped to 16% and 30%, respectively. On the other hand, at baseline, no patient in the TH group and only 2% of the patients in the MA group had mild disease, and this percentage increased to 16% at Week 4 for both groups (Table 2).

OMERACT-OARSI criteria of response. There was no significant difference between the TH and MA group responses according to the OMERACT-OARSI criteria in the study (p = 0.54). The response rate at Week 4 was 74% in the TH group and 72% in the MA group, rates that were sustained until the end of the study (Figure 3D).

There were no differences between the groups in all efficacy outcomes regarding the presence of the aspirated joint fluid.

Efficacy comparisons are summarized in Table 2.

Safety. There was only 1 adverse event in the MA group, which was postinjection arthritis in the day following the procedure, characterized by pain, swelling, redness, and joint effusion. The patient completely recovered after arthrocentesis, rest, and NSAID treatment. No adverse events were reported in the TH group.

DISCUSSION

Our present study provided strong evidence that TH and MA IA injections are equally effective in reducing knee pain and promoting function improvement in patients with knee OA who failed to control symptoms with analgesics or NSAID.

In this randomized, double-blind study, efficacy comparisons were carried out in a large knee OA population during 24 weeks. In our study, more patients were included and the followup was longer than the 8-week period of the only other previous head-to-head trial[10]. In addition, the present study included the OMERACT-OARSI criteria in the evaluation of response, as well as other outcome measures, such as patients' assessment of pain, PtGA and PGA of disease, the WOMAC questionnaire, and the LI. Although the previous study used some of these evaluations, only in our present study were they used concomitantly. Another advantage of our present study is that the same dose of TH and MA was evaluated. The 40-mg dose of TH and MA has the glucocorticoid potency equivalent to 50 mg of prednisone that is suggested to be associated with longer term benefits[19].

Most patients achieved OMERACT-OARSI criteria of response. An improvement in pain and function was observed herein in the short term with both corticosteroids, which is in accordance with previous studies[6]. This beneficial effect was sustained until the end of the study at Week 24. Few studies have addressed the longterm efficacy of IA corticosteroid injections, but a metaanalysis revealed a possible benefit of up to 24 weeks[19]. Only for PtGA of disease was the benefit achieved at Week 4 not sustained at Week 24.

In contrast to the present study, Pyne, *et al*[10] compared TH and MA and found that TH was more effective in reducing pain by VAS at Week 3, but only MA maintained benefit at Week 8. However, in that study, different doses of corticosteroids were used (TH 20 mg and MA 40 mg) that may have influenced the results.

On the other hand, Yavuz, *et al*[20] performed a 12-week randomized, placebo-controlled trial that compared 3 IA corticosteroid preparations (triamcinolone acetonide, MA, and betamethasone disodium phosphate) and found that MA had a better analgesic effect until the sixth week, while no difference in the LI was observed among the active groups during the trial. In contrast to our study, triamcinolone acetonide was used instead of TH. Further, patients with KL grade IV (severe disease) were included in that trial population, which could explain the different findings. In our study, only patients with OA who scored KL grades II and III were included in the study population, because a more severe disease would be less likely to respond to IA corticosteroids, as previously demonstrated[21].

However, our present study has some limitations. No control group was used for comparisons. Because of the previously demonstrated efficacy of IA corticosteroids[6] in knee OA, a control group would not be approved by the local ethics committee. Another point refers to the long time to

recruit study subjects. The eligibility criteria, the referral of patients from only 1 Department of Rheumatology, and the requirement to screen and randomize subjects in the same day, were responsible for this long period of time. Another limitation is that the MA group received IA lidocaine while the TH group did not. This was used to keep the blindness because of the different steroid concentrations. Also, it was assumed that lidocaine would not interfere in the study analyses because of its short half-life. The small number of subjects with joint effusion is another point. In fact, the 22-gauge 1 1/4″ needle used for joint injection is not the most appropriate for arthrocentesis. Because the procedures were not performed under imaging guidance, it could be inferred that the medication was not injected intraarticularly for some subjects. To minimize this problem, the same experienced rheumatologist performed all the joint injections[22]. Regarding the study population, the initial pain VAS score was higher than other similar studies[10,20]. However, in contrast to those studies, only patients with OA symptoms that were not adequately controlled by analgesics and/or NSAID were eligible for our present study.

Finally, our results differ from those observed in rheumatoid arthritis (RA) studies, where the superiority of TH compared with MA was demonstrated[23,24]. OA and RA have distinct pathophysiological mechanisms, and synovial histology studies with synovitis grading scores reveal that the synovitis of OA is low-grade while in RA it is high-grade, which could explain the different results[25,26]. Additionally, sonographic and clinical synovitis were not found to be predictors of response to IA corticosteroids in knee OA[27,28].

To our knowledge, this is the first head-to-head study to demonstrate that IA TH and MA are equally effective in the treatment of patients with symptomatic knee OA. Pain relief and functional improvement can be achieved after a single injection of both steroid preparations and be sustained for as long as 24 weeks. Further research should focus on predictors of response to corticosteroid knee injections.

ACKNOWLEDGMENT

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