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Original article

Intra-articular injection with triamcinolone hexacetonide in patients with rheumatoid arthritis: prospective assessment of goniometry and joint inflammation parameters

Rita Nely Vilar Furtado, Flávia Soares Machado, Karine Rodrigues da Luz, Marla Francisca dos Santos, Monique Sayuri Konai, Roberta Vilela Lopes, Jamil Natour*

Universidade Federal de São Paulo, Disciplina de Reumatologia, São Paulo, SP, Brazil

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ABSTRACT

Objectives: To evaluate local joint variables after intra-articular injection with triamcinolone hexacetonide in rheumatoid arthritis patients.

Methods: We blindly and prospectively (baseline, 1, 4, 12 and 24 weeks) evaluated metacarpophalangeal, wrist, elbow, shoulder, knee and ankle joints after triamcinolone hexacetonide intra-articular injection by the following outcome measures: visual analogue scale 0–10 cm (VAS) for rest pain (VASR); VAS for movement pain (VASM); VAS for joint swelling (VASSw); flexion (FlexG) and extension (ExtG).

Results: 289 patients (635 joints) were studied. VASSw ($p < 0.001$) and VASR ($0.001 < p < 0.016$) improved from T0 to T4, T12 and T24 for all joints. VASM improved from T0 to T4 ($p < 0.021$) for all joints; T0 to T12 ($p < 0.023$) for MCF and knee; T0 to T24 ($p < 0.019$) only for MCF and knee. FlexG improved from T0 to T4 ($p < 0.001$) for all joints; T0 to T12 ($p < 0.001$) and T0 to T24 ($p < 0.02$) only for MCF and knee. ExtG improved from T0 to T4 ($p < 0.001$) for all joints except for elbow; T0 to T12 ($p = 0.003$) for wrist, metacarpophalangeal and knee; and T0 to T24 ($p = 0.014$) for MCF and knee.

Conclusion: VASSw responded better at short and medium term after IAI with triamcinolone hexacetonide in our sample of RA patients.

* *Corresponding author.*
E-mail: rvfurtado@hotmail.com (R.N. Furtado).

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Injeção intra-articular de hexacetonido de triancinolona em pacientes com artrite reumatoide: avaliação prospectiva da goniometria e parâmetros de inflamação articular

Palavras-chave:
Artrite reumatoide
Injeções intra-articulares
Triamcinolona
Melhoria

RESUMO

Objetivos: Avaliar variáveis articulares locais após a infiltração intra-articular (IIA) de hexacetonido de triancinolona (HT) em pacientes com artrite reumatoide (AR).
Métodos: Foram avaliadas, de modo cego e prospectivo (nos tempos inicial, 1, 4, 12 e 24 semanas), as articulações metacarpofalângica (MCF), punho, cotovelo, ombro, joelho e tornozelo após a IIA de HT utilizando-se das seguintes medidas de desfecho: escala visual analógica (EVA) de 0 a 10 cm para dor em repouso (EVAr); EVA para dor ao movimento (EVAm); EVA para edema articular (EVAe); flexão (FlexG) e extensão (ExtG).
Resultados: Estudaram-se 289 pacientes (635 articulações). A EVAe ($p < 0{,}001$) e a EVAr ($0{,}001 < p < 0{,}016$) melhoraram de T0 a T4, T12 e T24 em todas as articulações. A EVAm melhorou de T0-T4 ($p < 0{,}021$) em todas as articulações; T0-T12 ($p < 0{,}023$) na MCF e no joelho; T0-T24 ($p < 0{,}019$) apenas na MCF e no joelho. A FlexG melhorou de T0-T4 ($p < 0{,}001$) em todas as articulações; T0-T12 ($p < 0{,}001$) e T0-T24 ($p < 0{,}02$) apenas na MCF e no joelho. A ExtG melhorou de T0-T4 ($p < 0{,}001$) em todas as articulações, exceto no cotovelo; T0-T12 ($p = 0{,}003$) no punho, na MCF e no joelho; e T0-T24 ($p = 0{,}014$) na MCF e no joelho.
Conclusão: A EVAe respondeu melhor em curto e médio prazos após a IIA de HT nessa amostra de pacientes com AR.

Introduction

Intra-articular injection (IAI) with corticosteroids (CEs) has been a very common practice among rheumatologists since 1951.[1] It is usually used when mono or pauci-articular synovitis persists.[2]

There are several CEs used in clinical practice. However, over the decades, it has been observed in pharmacokinetic studies that the CE with more microcrystalline properties remains longer in the joint.[3]

Thus, since 1961 triamcinolone esters have been used in IAI for the treatment of refractory synovitis.[2] Triamcinolone hexacetonide (TH) is the fluorinated CE with the lowest solubility and most atrophying properties among the CEs.[3] However, it is less utilized in comparison with other less atrophying CEs.[4–6] Although IAI is widely used in clinical practice among rheumatologists, little is known about predictors and local variables (pain, swelling and goniometry) of best response to IAI.

The aim of this study was to assess the response of variables such as joint pain, swelling and goniometry after IAI with TH in short and medium terms in rheumatoid arthritis (RA) patients.

Materials and methods

A prospective study was conducted in a cohort of 289 adult RA patients[7] with refractory synovitis who received TH IAI.

Patients were recruited from outpatient RA clinic from the Rheumatology Division of the Universidade Federal de Sao Paulo, Sao Paulo, Brazil. The Ethics Committee of this institution approved this study.

Inclusion criteria were: RA diagnosis according to the American College of Rheumatology (ACR)[7]; age between 18 and 65 years; refractory synovitis (persistent pain and swelling) in at least one of the following joints: metacarpophalangeal (MCP), wrist, elbow, shoulder, knee or ankle; functional class II or III[8]; stable dose of DMARD for the past three months; and stable dose of CE in the last month. Patients were excluded if there was any suspicion of local or systemic infection; severe clotting disorder; received any IAI in the past 3 months before the study, or were clinically decompensated from diseases such as diabetes mellitus or hypertension. All patients have read, understood and agreed to sign the informed consent form.

Intervention

IAI with TH was blindly performed after rigorous antisepsis with topical povidone-iodine. We used sterile and disposable materials in all IAIs. The procedure was performed on a single occasion (T0–baseline) by the same rheumatologist with 20 years of experience in interventional rheumatology.

The doses of TH used varied according to each joint: shoulder, 80 mg (4 mL); elbow 40 mg to 60 mg (2–3 mL); wrist, 30–40 mg (1.5–2 mL); MCP joint, 10–20 mg (0.5–1 mL); knee, 40–80 mg (2–4 mL), ankle, 40–60 mg (2–3 mL).[9] The patients underwent mono, pauci (up to 3 joints) or poly (4–8 joints) IAI according to the number of joints with refractory synovitis at the time of enrollment.

Assessment

Patient assessment was performed by a blinded observer, unaware of the demographic characteristics of the joint disease and baseline variables of patients.

The assessment times were: T0 (baseline), T1 (1 week), T4 (4 weeks), T12 (12 weeks) and T24 (24 weeks) after the IAI.

The following assessment instruments were used at each time of assessment: VAS (visual analogue scale, 0–10 cm) for joint pain at rest (VASR), VAS for joint pain during motion (VASM), VAS for joint swelling (VASSw); goniometry for flexion (FlexG) and extension (ExtG) for all joints studied. The shoulder was not assessed for extension.

Statistical analysis

The continuous variables were described in mean and standard deviation (SD) and the categorical variables in frequencies and percentages.

Comparison of these percentages with continuous baseline variables was made using Kruskal–Wallis test, while comparison with baseline categorical variables was done using Chi-square or Fisher's Exact test. These tests were used only for same baseline demographic variables and not used in the comparison of the repeated variables. For the assessment of times of the most important continuous variables of the present study, e.g. VASR, VASM, VASSw, FlexG and ExtG, we used ANOVA with repeated measures. All statistical analyses for these variables assessed at time points were carried out using ANOVA test with repeated measures.

p values were considered statistically significant under 0.05.

Results

Two hundred and eighty-nine RA patients were studied prospectively, with a mean age of 47.6 years (±10.8); mean disease duration of 10.98 years (±8.4); 48.5% of the sample was Caucasian and the women to men ratio was 12:1. Six hundred and thirty-five joints were included and studied between T0 and T4, and 313 joints until T24. All joints assessed until T4, were also evaluated at T1, and all those assessed at T24 were also evaluated at T12.

We found no significant differences in the proportion of left and right sides in the joints studied ($p = 0.302$, Chi-square test). Also, we found no significant differences in age distribution among the different joints ($p = 0.064$, Kruskal–Wallis test).

The most studied joints at inclusion were wrists (160) and the least studied were shoulders (35). On the other hand, the joints most assessed at T24 were MCP joints (103). The variables studied at T0; the distribution of mono and pauci or poly-IAI and the number of assessed joints until T4 and T24 are shown in Table 1.

Tables 2–6 show the results of statistical analysis for response to IAI with TH for each variable, VASR, VASM, VASSw, FlexG and ExtG. Statistical analysis was performed comparing the time of assessment with T0 (baseline) for each variable.

VASR showed a very good response to IAI with TH and a statistically significant improvement from T0 to T4 ($p < 0.001$); T0 to T12 ($p < 0.012$); and T0 to T24 ($p < 0.016$) for all joints studied. The improvement of the elbow from T0 to T12, and elbow and ankle from T0 to T24 were those rates with the lowest statistical significance. This analysis is shown in Table 2.

Table 1 – Demographic, related to disease and related to injection data of the baseline sample.

Variables	
Age in years, mean (±SD)	47.64 (±10.8)
Disease duration in years, mean (±SD)	10.98 (±8.4)
Women: Men ratio	12:1
Global pain, VAS mean (±SD)	6.52 (±1.7)
HAQ, mean (±SD)	1.36 (0.6)
White skin color *N* (%)	308 (48.5)
Functional Class II N (%)/III N (%)	360 (56.7)/275 (43.3)
Monoarticular injetion N (%)	300 (47.2)
Pauciarticular injection N (%)	68 (23.5)
Poly-articular injection N (%)	312 (49.1)
Rheumatoid Factor positivity N (%)	416 (65.6)
Extra-articular disease N (%)	71 (11.2)
Previous IAIC N (%)	300 (47.2)
Number of joints through T4/T24:	
Shoulder *N*	35/0
Elbow *N*	48/17
Wrist *N*	160/63
MCP *N*	142/103
Knee *N*	152/85
Ankle *N*	98/45
Patients/Joints evaluated from T0 to:	
T4	289/635 joints
T12	185/403 joints
T24	35/313 joints

HAQ, Health Assessment Questionnaire; *N* (%), frequency (percentage); SD, standard deviation; IAIC, intra-articular injection with corticosteroid; MCP, metacarpophalangeal; VAS, visual analogue scale.

VASM presented the worst evolution compared to VASR in the same joints. VASM showed improvement from T0 to T4 ($p < 0.001$) for all joints studied; from T0 to T12 ($p < 0.023$) for the wrist, MCP and knee; and from T0 to T24 ($p < 0.019$) only for MCP and knee. The elbow was the only joint which VASM did not improve after the IAI with TH from T0 to T24. The ankle did not improve from T0 to T12, and the ankle and the wrist showed no improvement from T0 to T24 (Table 3).

VASSw showed the best performance for all joints, at all assessment times, as seen in Table 4. This variable improved statistically from T0 to T4 ($p < 0.001$); T0 to T12 ($p < 0.001$); and T0 to T24 ($p < 0.001$) for all joints, with the highest statistical significance ($p < 0.001$) (Table 4).

Joint goniometry responded worst to IAI with TH compared to the other variables. FlexG improved from T0 to T4 ($p < 0.001$) for all the joints. However, this improvement occurred only for MCF and knee from T0 to T12 ($p < 0.001$) and from T0 to T24 ($p < 0.011$). In other words, in the medium term, this improvement was not sustained. These data are seen in Table 5.

ExtG also responded worst to the IAI with TH compared to pain and joint swelling. ExtG improved from T0 to T4 ($p < 0.001$) for all joints except for the elbow; from T0 to T12 ($p < 0.003$) for the wrist, MCP and knee; and from T0 to T24 ($p < 0.014$) for MCP and knee (Table 6).

Discussion

IAI is used for short-term treatment of refractory synovitis, mainly mono and pauci-articular. TH is the CE with the

Table 2 – Assessment of improvement in joint pain at rest (VASR) over time for each joint studied.

Joint	VASR – Mean (±SD)								
	T0	T1	*p*	T4	*p*	T12	*p*	T24	*p*
Shoulder									
T0–T4 (*n* = 35)	5.42 (1.75)	1.68 (2.63)	<0.001	0.80 (1.93)	<0.001	–	–	–	–
Elbow									
T0–T4 (*n* = 48)	4.97 (2.50)	1.08 (1.85)	<0.001	0.77 (1.65)	<0.001	–	–	–	–
T0–T24 (*n* = 17)	4.11 (3.47)	1.35 (2.14)	0.011	1.00 (1.83)	0.001	1.82 (2.74)	0.012	1.58 (2.39)	0.016
Wrist									
T0–T4 (*n* = 160)	4.69 (2.54)	2.06 (2.36)	<0.001	1.52 (2.17)	<0.001	–	–	–	–
T0–T24 (*n* = 63)	3.34 (3.15)	0.88 (1.85)	<0.001	0.74 (1.66)	<0.001	1.98 (2.73)	0.004	1.82 (2.39)	<0.001
MCP									
T0–T4 (*n* = 142)	2.98 (2.72)	0.98 (1.91)	<0.001	0.54 (1.50)	<0.001	–	–	–	–
T0–T24 (*n* = 103)	2.24 (2.76)	0.94 (2.01)	<0.001	0.48 (1.60)	<0.001	0.76 (2.07)	<0.001	0.79 (1.94)	<0.001
Knee									
T0–T4 (*n* = 152)	5.98 (2.29)	1.98 (2.22)	<0.001	2.23 (3.30)	<0.001	–	–	–	–
T0–T24 (*n* = 85)	5.83 (2.62)	1.94 (2.20)	<0.001	2.40 (2.61)	<0.001	2.77 (2.79)	<0.001	3.92 (3.06)	<0.001
Ankle									
T0–T4 (*n* = 98)	4.59 (2.65)	1.33 (2.16)	<0.001	1.42 (2.43)	<0.001	–	–	–	–
T0–T24 (*n* = 45)	3.56 (3.15)	1.36 (2.21)	<0.001	1.56 (2.63)	0.001	1.72 (2.38)	0.001	2.38 (2.80)	0.014

VASR, visual analogue scale 0–10 cm for rest pain; SD, standard deviation; MCP, metacarpophalangeal joint.
Statistical test: ANOVA for repeated measures.

slowest joint clearance and the most potent in producing synovial atrophy. However, it is also the most potential to cause damage if injected into extra-articular tissue.[3] It has been proven its superiority over other intraarticular CE used in RA and in osteoarthritis (OA) patients. Its use has been considered superior to the use of systemic CE when used in mono or poly IAI in RA patients.[10,11]

Although it is a procedure widely used by rheumatologists, there are few prospective studies comparing the effectiveness of IAI with other interventions, or even with the systemic use of other CE.[10,11]

By conducting this study, we intended to identify the joint variables which best responded to IAI with TH in the joints we considered relevant in RA patients, using "blinded" and prospective assessments at short and mid-term.

It was observed that VASR improved from T0 to T4, T0 to T12 and T0 to T24 for all injected joints. We expected the rest pain to be a variable well responsive to the IAI. Surprisingly, VASM improved statistically for all joints only in the short term (T0–T4). In the long term, this variable improved statistically, for only MCPs and knees. The difference in pain response between VASR and VASM may be due to several factors. Pain on movement may be a more difficult variable to treat because of the stress resulting from the movement of the inflamed joint.

Joint goniometry variables (FlexG and ExtG) responded well to IAI with TH only in the short term, where statistical

Table 3 – Assessment of improvement in joint pain in motion (VASM) over time for each joint studied.

Joint	VASM – Mean (±SD)								
	T0	T1	*p*	T4	*p*	T12	*p*	T24	*p*
Shoulder									
T0–T4 (*n* = 35)	7.11 (1.62)	4.74 (2.47)	<0.001	3.31 (2.71)	<0.001	–	–	–	–
Elbow									
T0–T4 (*n* = 48)	5.70 (3.29)	2.66 (2.83)	<0.001	1.93 (2.60)	<0.001	–	–	–	–
T0–T24 (*n* = 17)	2.05 (2.53)	0.88 (1.96)	NS	0.58 (1.66)	NS	0.29 (1.21)	NS	0.58 (1.66)	NS
Wrist									
T0–T4 (*n* = 160)	4.76 (3.11)	2.69 (2.67)	<0.001	2.28 (2.57)	<0.001	–	–	–	–
T0–T24 (*n* = 63)	1.74 (2.40)	0.55 (1.58)	<0.001	0.79 (1.84)	0.021	0.82 (1.83)	0.023	1.66 (2.37)	NS
MCP									
T0–T4 (*n* = 142)	2.93 (3.18)	1.38 (2.19)	<0.001	1.02 (2.01)	<0.001	–	–	–	–
T0–T24 (*n* = 103)	1.50 (2.30)	0.63 (1.66)	0.012	0.33 (1.26)	<0.001	0.38 (1.34)	<0.001	0.67 (1.72)	0.019
Knee									
T0–T4 (*n* = 152)	6.16 (2.37)	2.40 (2.37)	<0.001	2.11 (2.39)	<0.001	–	–	–	–
T0–T24 (*n* = 85)	5.52 (2.69)	1.81 (2.22)	<0.001	1.91 (2.49)	<0.001	2.56 (2.66)	<0.001	3.51 (3.18)	<0.001
Ankle									
T0–T4 (*n* = 98)	5.30 (3.28)	2.85 (2.91)	<0.001	2.80 (3.05)	<0.001	–	–	–	–
T0–T24 (*n* = 45)	2.44 (2.52)	0.77 (1.83)	0.003	0.88 (1.93)	0.002	1.66 (2.38)	NS	2.22 (2.51)	NS

VASM, visual analogue scale 0–10 cm for pain in motion; SD, standard deviation; NS, no statistical difference; MCP, metacarpophalangeal joint.
Statistical test: ANOVA for repeated measures.

Table 4 – Assessment of improvement in joint swelling (VASSw) over time for each joint studied.

Joint	VASSw – Mean (±SD)								
	T0	T1	*p*	T4	*p*	T12	*p*	T24	*p*
Shoulder									
T0–T4 (*n* = 35)	3.37 (1.64)	1.31 (0.99)	<0.001	0.62 (0.77)	<0.001	–	–	–	–
Elbow									
T0–T4 (*n* = 48)	5.47 (1.32)	2.04 (1.85)	<0.001	1.43 (1.72)	<0.001	–	–	–	–
T0–T24 (*n* = 17)	5.47 (2.18)	1.17 (2.18)	<0.001	1.47 (2.34)	<0.001	1.47 (2.33)	<0.001	0.88 (1.96)	<0.001
Wrist									
T0–T4 (*n* = 160)	5.27 (1.32)	2.83 (2.08)	<0.001	2.23 (2.09)	<0.001	–	–	–	–
T0–T24 (*n* = 63)	5.27 (1.32)	2.46 (2.51)	<0.001	1.98 (2.46)	<0.001	3.33 (2.37)	<0.001	3.57 (2.27)	<0.001
MCP									
T0–T4 (*n* = 142)	5.07 (0.84)	2.05 (2.23)	<0.001	1.25 (1.92)	<0.001	–	–	–	–
T0–T24 (*n* = 103)	5.07 (0.84)	1.99 (2.45)	<0.001	1.21 (2.15)	<0.001	1.85 (2.41)	<0.001	1.99 (2.45)	<0.001
Knee									
T0–T4 (*n* = 152)	4.58 (1.68)	1.93 (1.81)	<0.001	1.30 (1.54)	<0.001	–	–	–	–
T0–T24 (*n* = 85)	4.17 (1.66)	1.48 (1.91)	<0.001	1.05 (1.57)	<0.001	1.17 (1.64)	<0.001	1.50 (1.78)	<0.001
Ankle									
T0–T4 (*n* = 98)	5.56 (1.45)	2.71 (2.12)	<0.001	2.31 (2.09)	<0.001	–	–	–	–
T0–T24 (*n* = 45)	5.47 (1.32)	2.11 (2.49)	<0.001	1.88 (2.45)	<0.001	2.66 (2.52)	<0.001	2.77 (2.51)	<0.001

VASSw, visual analogue scale 0–10 cm for joint swelling; SD, standard deviation; MCP, metacarpophalangeal joint.
Statistical test: ANOVA for repeated measures.

responses to all joints studied were observed. However, in the medium term, the responses were statistically more fragile and in a fewer number of joints. This finding may be due to the fact that our sample was composed by RA patients with a mean length time of disease of almost 11 years. The high prevalence of long standing RA probably represented a crucial factor for the goniometry outcomes. Long standing patients like these may present severe structural damage and secondary osteoarthritis and this may have influenced the response of goniometry variables FlexG and ExtG as well as VASM.

VASSw was the variable with the best response to IAI with TH at all assessment times for all joints, and with best statistical significance. We observed a statistical improvement from T0 at T4, T12 and T24 weeks for all joints, always with a $p < 0.001$. This reinforces the hypothesis of the atrophying properties of TH, possibly causing a decrease in VASSw, a joint parameter more objective than the pain.

In the literature, we found that the IAI response duration may vary according to the disease in question. It is observed in meta-analyses and systematic reviews that the typical response duration to IAI in OA patients is (typically) from

Table 5 – Assessment of improvement in joint flexion over time for each joint studied.

Joint	Joint flexion in degrees – Mean (±SD)								
	T0	T1	*p*	T4	*p*	T12	*p*	T24	*p*
Shoulder									
T0–T4 (*n* = 35)	137.42 (32.50)	148.25 (31.85)	<0.001	156.14 (32.99)	<0.001	–	–	–	–
Elbow									
T0–T4 (*n* = 48)	124.72 (12.20)	132.08 (10.14)	<0.001	133.16 (8.45)	<0.001	–	–	–	–
T0–T24 (*n* = 17)	126.17 (10.82)	130.58 (11.97)	NS	127.35 (6.40)	NS	126.47 (10.27)	NS	128.52 (7.01)	NS
Wrist									
T0–T4 (*n* = 160)	42.46 (18.70)	45.57 (21.10)	0.005	47.73 (19.16)	<0.001	–	–	–	–
T0–T24 (*n* = 63)	45.87 (22.31)	47.22 (24.86)	NS	48.73 (21.53)	NS	48.53 (22.66)	NS	46.50 (20.62)	NS
MCP									
T0–T4 (*n* = 142)	76.72 (18.63)	83.57 (10.65)	<0.001	85.03 (9.40)	<0.001	–	–	–	–
T0–T24 (*n* = 103)	82.28 (10.65)	84.56 (9.26)	0.007	85.09 (9.54)	<0.001	85.19 (9.94)	<0.001	84.51 (11.42)	0.011
Knee									
T0–T4 (*n* = 152)	116.01 (15.07)	121.25 (15.59)	<0.001	123.49 (17.26)	<0.001	–	–	–	–
T0–T24 (*n* = 85)	115.94 (13.82)	120.14 (17.36)	0.009	122.17 (14.22)	<0.001	121.29 (13.02)	<0.001	120.14 (14.26)	0.002
Ankle									
T0–T4 (*n* = 98)	28.59 (13.91)	32.34 (13.26)	<0.001	32.85 (14.51)	<0.001	–	–	–	–
T0–T24 (*n* = 45)	33.11 (16.42)	34.22 (16.05)	NS	31.77 (16.99)	NS	33.22 (17.22)	NS	32.00 (16.69)	NS

SD, standard deviation; NS, no statistical difference; MCP, metacarpophalangeal joint.
Statistical test: ANOVA for repeated measures.

Table 6 – Assessment of improvement in joint extension over time for each joint studied.

Joint	Joint extension in degrees – Mean (±SD)								
	T0	T1	*p*	T4	*p*	T12	*p*	T24	*p*
Elbow									
T0–T4 (*n* = 48)	−4.79 (18.67)	−2.39 (13.87)	NS	−2.04 (15.23)	NS				
T0–T24 (*n* = 17)	8.52 (20.67)	5.58 (15.50)	NS	6.47 (15.81)	NS	6.17 (15.36)	NS	5.88 (13.92)	NS
Wrist									
T0–T4 (*n* = 160)	41.58 (20.35)	45.34 (19.75)	<0.001	47.46 (20.18)	<0.001				
T0–T24 (*n* = 62)	58.54 (17.16)	60.72 (17.94)	NS	60.64 (20.87)	NS	63.95 (16.72)	<0.001	60.48 (17.54)	NS
MCP									
T0–T4 (*n* = 142)	62.55 (34.23)	65.66 (32.62)	<0.001	66.93 (31.60)	<0.001				
T0–T24 (*n* = 77)	82.20 (10.74)	84.74 (9.13)	0.016	85.19 (9.43)	0.001	85.32 (9.50)	0.003	84.93 (11.39)	0.014
Knee									
T0–T4 (*n* = 152)	−3.73 (8.34)	0.44 (6.19)	<0.001	0.46 (5.48)	<0.001				
T0–T24 (*n* = 85)	−2.68 (8.79)	3.09 (5.65)	<0.001	2.82 (4.96)	<0.001	3.76 (6.66)	<0.001	4.30 (6.87)	<0.001
Ankle									
T0–T4 (*n* = 98)	11.29 (4.85)	13.17 (5.15)	<0.001	14.38 (5.46)	<0.001				
T0–T24 (*n* = 45)	13.56 (5.10)	13.84 (5.87)	NS	14.77 (5.70)	NS	14.09 (4.97)	NS	12.54 (6.41)	NS

SD, standard deviation; NS, no statistical difference; MCP, metacarpophalangeal joint.
Statistical test: ANOVA for repeated measures.

only one to two weeks, reported a maximum of 4 weeks.[12–14] These results are quite different from ours, which showed sustained response (improvement) to IAI with TH for at least four weeks for all variables in all assessed joints. On assessing the VASs, most of the joints showed sustained response up to 12 weeks. For MCPs and knee joints, we observed sustained response until T24, not only for the three VASs variables, but also for the joint goniometry of flexion and extension.

As regards juvenile idiopathic arthritis (JIA), systematic reviews have shown a response to the CE IAI with a maximum duration of 1 year and 3 months to 1 year and 8 months, depending on the study. In these studies, the predictors of increased response to IAI were "current use of methotrexate", "knee injected", "use of TH for IAI" and "current use of CE at the time of IAI".[15–18] In our study, knee also showed an excellent response. But our follow-up time of patients was much shorter, only 24 weeks.

The joints that showed statistical improvement after IAI with TH for all variables and times points studied in our study were the MCPs and knees. This finding may be due, among other causes, to the excellent accuracy of the IAI in those joints, as determined by Lopes et al.[19] These authors found an accuracy of 100% and 97% for IAIs with TH performed blindly and respectively for knees and MCPs.

We can point some limitations of the present study. We can mention the intragroup analysis; the non-homogeneous distribution of the kinds of injected joints (particularly the low number of shoulders) and follow-up time; the lack of a functional assessment (ex: HAQ) at the time-points; the lack of long-term follow-up. The following are also limitations of the present study: the absence of analysis between pre-injected and fist-injected joints, the absence of analysis of injection accuracy and the absence of analysis of the correlation between the use of antirheumatic drugs and the presence of articular deformity with the response to IAI; and, moreover, the absence of a more objective assessment tool, such as the articular ultrasound. The absence of any method of statistical correction for multiple comparisons can also be considered a limitation.

Moreover, the applicability of our work is relevant. Through it, we identified that joint swelling is the variable that best responds to IAI with TH in a large cohort of patients evaluated prospectively and "blindly". This reinforces the indication of TH use to promote chemical synovectomy in RA patients with refractory synovitis. Another interesting finding in our study is the evidence of a poor response in joint goniometry in the medium term after IAI with TH. Therefore, we should not always expect significant changes in joint goniometry after IAI with CE, even in joints that improved pain and swelling.

This study corroborates the statement of IAI with TH for treatment of refractory synovitis in RA patients. Joint swelling was identified as the variable with the best response to this procedure, and the knees and MCPs as the joints with the best response to it. More prospective studies are required to define other variables such as the optimal dose of TH and the exact duration of response after IAI.

Conflicts of interest

The authors declare no conflicts of interest.

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