Monoarticular corticosteroid injection versus systemic administration in the treatment of rheumatoid arthritis patients: a randomized double-blind controlled study

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Abstract

Objective

To compare the efficacy and safety of intraarticular glucocorticoid injection to its systemic use for treatment of knee synovitis in rheumatoid patients.

Methods

A randomized double-blind controlled study was conducted including 60 patients with RA. Patients were randomized to receive either a single intraarticular knee injection with triamcinolone hexacetonide 60 mg (3 ml) and xylocaine chloride 2% (1 ml) associated to a single intramuscular injection of 1 ml of xylocaine chloride 2% (IAI group) or 1 ml of xylocaine chloride 2% by intraarticular injection and a intramuscular injection of triamcinolone acetonide 60 mg (3 ml) and xylocaine chloride 2% (1 ml) (IM group). All patients were blindfolded for the procedure. Evaluations were performed at baseline and 1, 4, 8 and 12 weeks post-intervention. The following instruments were used: VAS for knee pain, as primary outcome, VAS for knee morning stiffness and edema; the ACR 20, 50 and 70% improvement criteria; knee circumference and goniometry; Likert's scale of improvement; daily use of oral glucocorticoid and NSAIDs, blood pressure and adverse effects.

Results

Patients in the IAI group had significantly better results for VAS for knee pain, edema and morning stiffness as well as for improvement evaluation after intervention according to the patient ($p<0.001$) and physician ($p=0.02$).

Conclusion

Our results demonstrate that intraarticular injection with glucocorticoids is superior to its systemic use for the management of monoarticular synovitis in rheumatoid patients. The intraarticular approach showed better results in terms of local inflammatory variables and improvement evaluation by the patient and physician.

Key words

Rheumatoid arthritis, glucocorticoids, intraarticular injection and synovitis.

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Introduction

Rheumatoid Arthritis (RA) is mainly characterized by chronic symmetric erosive polyarthritis. The "pannus" observed in this disease is responsible for progressive damage to the articular cartilage, the subchondral bone and ligaments, which in turn lead to deformity, loss of quality of life and disability (1, 2).

Given the considerably high morbidity and mortality, RA therapeutic regimes currently tend to be more aggressive and dynamic with the clear purpose of modifying the course of the disease aiming to prevent functional damage and deformities. That is now achieved by early and combined introduction of Disease Modifying Antirheumatic Drugs (DMARDs), biological agents targeting pro-inflammatory cytokines (*e.g.* anti-TNF drugs) and the restrictive use of non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids to situations of articular flare (3-6). Other important tools in the management of patients with RA include rehabilitation strategies and articular procedures such as chemical (intraarticular injections), radioisotopic and surgical synovectomies (5, 7).

Intraarticular injections are particularly recommended for RA patients with refractory mono or oligoarthritis. In this scenario, intraarticular injections are a very attractive alternative to increases in the systemic doses of glucocorticoids, often given orally or by parenteral administration (3-5, 8, 9).

Intraarticular injections, also known as "synoviorthoses", are performed by allocation of drugs in the intraarticular space aiming to control local inflammation and to promote atrophy of the synovial "pannus" (5, 8, 9). Several anti-inflammatory and anti-proliferative drugs have been administered by intraarticular injection, including the most recent biological agents (10-15). So far, glucocorticoids remain the most used and studied drugs for this procedure (5, 9, 16). Triamcinolone hexacetonide remains longer in the intraarticular environment and is the most recommended glucocorticoid for intraarticular injection especially due to its insolubility and high atrophying effect (17, 18). Controlled chemical synovectomy trials in RA patients have demonstrated that triamcinolone hexacetonide is superior to other glucocorticoids (19-23). According to McCarty *et al.*, chemical synovectomy with triamcinolone hexacetonide was able to improve arthritis for periods ranging from 3 to 21 months (18). Intraarticular injections with glucocorticoids have been used for decades to control oligoarticular flares in RA patients. However, there is no solid evidence evaluating the efficacy and safety of intraarticular injections as compared to the systemic use of glucocorticoid in pauciarticular disease flare. It is believed that glucocorticoid intraarticular injection is faster and more effective to reduce articular inflammation when contrasted to transient increases in the systemic doses of glucocorticoids in these patients (5, 8, 16). Nonetheless, most of the studies published on the matter have compared the therapeutic effect of various glucocorticoid formulations for intraarticular use while the direct comparison between intraarticular and systemic glucocorticoids in this scenario has still not been carried out (16, 19-24).

In the present study, we compare the efficacy and safety of intraarticular glucocorticoid injection to intramuscular administration of the drug in RA patients with active knee synovitis.

Material and Methods

Patients

A prospective double-blind randomized controlled trial was designed to compare the effect of two different glucocorticoid treatment programs in RA patients with active knee synovitis. Patients were recruited in the period from July 2004 to December 2005, from the Rheumatology Outpatients Clinics at Universidade Federal de Sao Paulo, Sao Paulo, Brazil. All patients had RA according to the ACR criteria (25). Written informed consent was obtained from all subjects and the Universidade Federal de Sao Paulo's Ethics Committee approved the study.

Sample size was calculated having an α error of 5% and a study power of 95%, sample size was determined as 50 patients (25 patients in each arm of the

study). Five more patients in each group were added to compensate for eventual losses during the protocol and the total sample size was then 60 patients. Inclusion criteria were: RA diagnosed for more than 6 months; age between 18 and 65 years; functional class II or III according to the ACR criteria (26); VAS score for pain in the knee higher than 5; stable doses of oral corticosteroid for the last 30 days and stable doses of DMARDs for the last 3 months; and active synovitis at least in one knee for at least the 30 days. Patients with non-controlled diabetes mellitus or hypertension, bacterial infection of any site, blood coagulation disorders, skin lesion on the affected knee, history of previous surgical procedure in the knee, use of intramuscular glucocorticoids in the last 30 days and those who had undergone any site intraarticular injection in the last 3 months or knee injection in the last 6 months were all excluded from the study. It was allowed that the same patient was randomized twice since the contralateral knee was choose for treatment.

Intervention

Randomization table was used to secretly and equally allocate patients in two different intervention groups, as follows:

Intraarticular injection (IAI) group (30 knees): patients underwent a single intraarticular knee injection with a solution containing triamcinolone hexacetonide 60 mg (3 ml) (Triancil®), xylocaine chloride 2% (1 ml) associated to a single intramuscular injection (in the gluteus) of 1 ml of xylocaine chloride 2%. When articular effusion was present, systematic withdrawal of the liquid was performed before intraarticular drug injection. Patients were instructed to rest for the following 48 hours, being allowed to move only for physiological needs.

Intramuscular (IM) group (30 knees): Patients in this group had the same procedures as performed for the IAI group with inverted sequences of solutions. They received 1 ml of xylocaine chloride 2% by intraarticular injection and a combined intramuscular injection of a solution containing triamcinolone acetonide 60 mg (3 ml) (Theracort®) and xylocaine chloride 2% (1 ml).

All patients were blindfolded for the procedure. The same examiner performed all procedures for both groups and another examiner "blinded" for the procedures performed further evaluations. In the case of bilateral knee synovitis, the knee with the highest score at the VAS for pain was chosen for intraarticular injection.

A total of 5 evaluations were performed at baseline (T0) and 1 (T1), 4 (T4), 8 (T8) and 12 (T12) weeks post-intervention. The following instruments were used for patient's evaluations: the American College of Rheumatology 20%, 50 and 70% improvement criteria (ACR20, ACR50 and ACR70%) (27-29); Knee morning stiffness (time in minutes); VAS for pain in the injected knee (0-10 cm); VAS for articular swelling in the injected knee (0-10 cm); knee circumference (measured at the level of the superior surface of the patella - cm); knee goniometry (flexion and extension); Likert's scale of improvement (LSI) for the knee (much worse, a little worse, unchanged, a little better or much better), according to the patient (LSI-Patient) and to the physician (LSI-Physician) (30); improvement percentage for the injected knee according to the patient (0-100%); daily use of oral glucocorticoids (mg); daily use of non-steroidal anti-inflammatory drugs (NSAIDs, number of tablets); Lequesne's algofunctional index for knee (31) and clinical evaluation (number of contacts to the physician, systolic and diastolic blood pressure, number of hospital visits, number and type of adverse effects).

Patients were instructed not to change the dosis and kind of medication they were in use and were asked to take non-steroidal anti-inflammatory drugs (sodium diclofenac 50 mg) as the primary symptomatic medication for pain and avoid extra-use of oral glucocorticoids (prednisone). The use of parenteral glucocorticoids was also not allowed during the course of the study.

Statistical analysis

Student *t*-test was used to analyze numeric non-repeated variables while binomial test and Fisher's exact test were used for categorical variables. A two-way ANOVA analysis was performed to evaluate repeated numeric variables and Mann-Whitney test was applied for repeated non-parametric variables. The data were analyzed according to the intention-to-treat principle and patients with missing data had the previous evaluation data repeated. Significance level was set as $p<0.05$.

Results

Fifty-four patients were included and completed the study protocol. The n value in the tables refers to the number of treated knees in each group. Their mean age was 43.7±10.9 years. Most of the patients were female (96%), Caucasian (57%) and had mean disease duration of 8.6±5.4 years. No losses were observed during the follow up. Only three patients did not have all the evaluations proposed in the study design. One patient in the IAI group missed evaluations at T1 and T4, while two other patients in the IM group missed evaluations at T4 and T12, respectively.

Baseline clinical, demographic data and disease related parameters for patients included in the study are shown in the Tables I and II. No statistically significant difference was observed between groups at this time-point.

Table III shows local variables during the course of the protocol for RA patients with knee synovitis undergoing glucocorticoid intervention by intraarticular knee injection (IAI group) or intramuscular administration (IM group). Data demonstrate that patients in the IAI group had significantly better response for the variables VAS for knee pain, edema and morning stiffness as compared to patients in the IM group.

The therapeutic responses according to ACR criteria (ACR 20, 50 and 70%) in RA patients with knee synovitis undergoing glucocorticoid intervention and data regarding improvement percentage as reported by the patient are demonstrated in the Table IV. No statistically significant difference was observed between groups in terms of therapeutic response criteria and their sub items. However, patients receiving

Table I. Baseline clinical and demographic characteristics of the patients in the study.

Variables	IAI (n=30)	IM (n=30)	*p**
Age, years (mean±SD)	42.5 ± 11.5	44.9 ± 10.4	0.40
Gender (F/M)	30/0	28/2	0.98
Body Mass Index, kg/m^2 (mean±SD)	26.1 ± 5.2	24.2 ± 4.4	0.13
Caucasian (%)	56.7%	56.7%	1.00
Disease duration, years (mean±SD)	9.7 ± 5.4	7.6 ± 5.3	0.13
Functional class (II / III)	23/7	22/8	0.76
Chloroquine diphosphate (%)	9 (30)	5 (16.67)	0.22
Methotrexate (%)	27 (90)	24 (80)	0.47
Sulfasalazine (%)	2 (6.67)	3 (10)	1.00
Leflunomide (%)	4 (13.33)	2 (6.67)	0.67
Infliximab (%)	1 (3.33)	0	1.00
Sodium diclofenac (tablets/day)	0.4 ± 0.7	0.4 ± 0.8	1.00
Oral prednisone (mg/day)	6.7 ± 7.6	7.1 ± 6.0	0.82
Rheumatoid factor (+)	21 (70)	23 (76.7)	0.56
Anti-perinuclear antibody (+)	8 (26.7)	4 (16.7)	0.19
Previous intraarticular injection (%)	23 (76.67)	20 (66.67)	0.387

*Student *t*-test and binominal analysis; IAI: intraarticular injection group; IM: intra-muscular injection group; F: female; M: male.

Table II. Local variables and other disease related parameters in patients with knee synovitis according to glucocorticoid intervention at baseline.

Variables	IAI (n=30) (Mean±SD)	IM (n=30) (Mean±SD)	*p**
VAS for knee pain (0-10cm)	7.2 ± 1.5	6.9 ± 1.4	0.36
VAS for knee edema (0-10cm)	5.1 ± 1.6	5.1 ± 1.8	0.91
Knee morning stiffness (minutes)	30.9 ± 44.4	44.8 ± 61.4	0.51
Knee circumference (cm)	40.4 ± 5.0	39.1 ± 3.6	0.41
Flexion (degrees)	118.3 ± 13.5	118.6 ± 11.9	0.71
Extension (degrees)	7.3 ± 7.8	6.2 ± 6.6	0.72
Lequèsne score	17.3 ± 2.7	17.9 ± 2.7	0.49
Systolic blood pressure (mmHg)	126.0 ± 21.1	122.5 ± 18.9	0.57
Diastolic blood pressure (mmHg)	78.3 ± 11.8	74.7 ± 12.0	0.23
Erythrocyte sedimentation rate (mm) [a]	49.7 ± 35.0	40.9 ± 21.8	0.47
HAQ [a]	1.4 ± 0.5	1.5 ± 0.7	0.30
Tender joint count [a]	10.4 ± 7.8	11.0 ± 8.9	0.88
Swollen joint count [a]	8.2 ± 5.2	8.8 ± 5.8	0.74
Patient VAS global assessment [a]	6.6 ± 1.7	6.5 ± 2.1	0.99
Physician VAS global assessment [a]	5.4 ± 1.7	5.3 ± 1.8	0.95
VAS for global pain-patient [a]	7.1 ± 1.5	6.6 ± 2.1	0.47

VAS: visual analogue scale; HAQ: health assessment questionnaire. [a] Variables from the ACR20, 50 and 70% improvement criteria; *Mann-Whitney test; IAI: intraarticular injection group; IM: intramuscular injection group.

glucocorticoids by intraarticular injection presented significantly higher improvement percentage for the knee as compared to those to had intramuscular glucocorticoid administration.

Data regarding the daily use of sodium diclofenac and oral prednisone show no statistically significant difference between groups during the course of protocol.

There was no statistically significant difference between groups in terms of systolic and diastolic blood pressure as well as number of adverse effects and events.

Adverse effects observed in the present study were: hypertension (26.7% IAI; 16.7% IM), muscle cramp (3.3% IAI; 0 IM), nausea (6.7% IAI; 10% IM), epigastralgia (3.3% IAI; 0 IM), dizziness (3.3% IAI; 0 IM), fever (3.3% IAI; 3.3% IM), polyuria (3.3% IAI; 0 IM), acne (3.3% IAI; 0 IM), ecchymosis (0 IAI; 3.3% IM), dried mouth (0 IAI; 3.3% IM), pruritus (6.7% IAI; 0 IM), erythematous skin lesions (0 IAI; 6.7% IM), weight gain (0 IAI; 3.3% IM), irregular menses (0 IAI; 6.7% IM), hypermenorrhea (0 IAI;13.3% IM) and headache (0 IAI; 3.3% IM).

Other events observed during the course of the study included: urinary tract colic (6.7% IAI; 0 IM), facial paralysis (3.3% IAI; 0 IM), lower limb ulcer (3.3% IAI; 0 IM), teeth hypersensibility (3.3% IAI; 0 IM), and increased number of falls (6.7% IAI; 3.3% IM).

Local side effects were: pain at the site of articular injection (3.3% IAI; 0 IM), feeling of ligament instability in the knee (6.7% IAI; 0 IM) and post-intervention flare (3.3% IAI; 0 IM). Hypopigmentation or skin atrophy was not observed in the IAI group. One patient in the IM group had skin atrophy in the gluteal area after intramuscular injection. There was no statistically significant difference between groups in terms of local side effects.

Patients receiving intraarticular glucocorticoid injection or intramuscular administration did not differ in terms of number of contacts to the physician (30% IAI; 30% IM) and number of hospital visits (33.3% IAI; 36.7% IM).

Response to intervention was also checked using a Likert's scale of improvement (LSI) according to the patient and to the physician. As shown in Table V, patients in the IAI group had significantly better responses by both LSI-Patient and Physician as compared to patients the IM group.

At the end of the study, five patients in the IM group (16.67%) had significant synovitis in the knee and underwent intraarticular injection with triamcinolone 60 mg. None of the patients in the IAI group needed further intervention.

Discussion

The present study demonstrated that intraarticular glucocorticoids for the treatment of knee synovitis in RA is superior to its systemic administration and is associated with better and long lasting efficacy when compared to its systemic use.

Intraarticular injection was first described in 1951 and since then has been used as a therapeutic tool for the management of RA and many other rheumatic diseases (5, 8, 24, 32). Some evidence has been put together throughout the years point to indications for the use of intraarticular injection as well as other scenarios where it should be

Table III. Prospective evaluation of local variables in 60 RA patients with knee synovitis according to glucocorticoid intervention.

Time point (weeks)	IAI (n=30) mean±SD	IM (n=30) mean±SD	*p*
	VAS for knee pain (cm)*		
T0	7.2 ± 1.5	6.9 ± 1.4	0.375
T1	3.3 ± 2.3	3.7 ± 3.0	0.501
T4	2.6 ± 2.3	4.1 ± 2.9	**0.007**
T8	2.1 ± 2.3	4.3 ± 2.8	**0.036**
T12	2.6 ± 2.6	4.5 ± 2.7	**0.002**
	Knee morning stiffness (minutes)*		
T0	30.9 ± 44.4	44.8 ± 61.4	0.510
T1	6.4 ± 15.3	26.7 ± 54.0	**0.037**
T4	6.5 ± 13.2	9.6 ± 23.7	0.099
T8	4.7 ± 8.5	17.4 ± 47.5	0.818
T12	9.0 ± 17.9	17.9 ± 25.5	0.169
	VAS for knee edema (cm)**		**<0.01**
T0	5.1 ± 1.6	5.1 ± 1.8	
T1	2.5 ± 1.7	3.1 ± 2.5	
T4	1.8 ± 1.5	3.0 ± 2.1	
T8	1.5 ± 1.7	3.3 ± 2.1	
T12	1.8 ± 1.5	3.6 ± 1.9	
	Knee circumference (cm)**		0.298
T0	40.5 ± 5.0	39.1 ± 3.6	
T1	39.7 ± 5.4	38.6 ± 3.7	
T4	39.3 ± 5.2	37.0 ± 7.8	
T8	39.3 ± 5.1	38.7 ± 3.5	
T12	39.7 ± 5.1	38.9 ± 3.5	
	Flexion (degrees)**		0.51
T0	118.3 ± 13.5	118.6 ± 11.9	
T1	123.1 ± 13.5	123.1 ± 12.0	
T4	124.2 ± 13.6	120.9 ± 13.8	
T8	125.1 ± 12.5	121.1 ± 12.9	
T12	121.8 ± 13.9	118.3 ± 14.6	
	Extension (degrees)**		0.80
T0	7.3 ± 7.8	6.2 ± 6.6	
T1	4.0 ± 5.8	4.0 ± 7.0	
T4	3.5 ± 4.9	4.8 ± 7.0	
T8	3.3 ± 4.3	4.6 ± 6.4	
T12	4.3 ± 6.7	4.7 ± 6.2	
	Lequesne score**		0.55
T0	22.4 ± 28.2	17.9 ± 2.7	
T1	11.5 ± 4.5	13.1 ± 4.3	
T4	11.3 ± 4.5	13.5 ± 4.7	
T8	11.4 ± 3.7	13.7 ± 4.6	
T12	11.7 ± 4.6	14.3 ± 4.5	
	Improvement percentage (%)**		**<0.0001**
T1	63.6 ± 26.0	49.7 ± 28.0	
T4	74.1 ± 26.0	52.7 ± 31.1	
T8	77.8 ± 23.7	53.3 ± 32.0	
T12	77.5 ± 23.3	44.7 ± 30.7	

IAI: intraarticular injection group; IM: intra-muscular injection group; *Mann-Whitney test; **ANOVA for repeated measures.

avoided and its potential side effects (8, 32-35).

In spite of its use for more than 50 years as a routine rheumatological procedure, there is no conclusive evidence comparing intraarticular glucocorticoid injection to its systemic administration for the management of mono or oligoarticular flares in RA patients.

Trends for the current management of RA point for early introduction of Disease Modifying Antirheumatic Drugs (DMARDs) associated with biological agents even for early stage disease. Intraarticular injection with glucocorticoids is also recommended as part of the treatment according to ACR guidelines, including the management of patients with early disease (6, 36-38).

Several glucocorticoids have been used for intraarticular injection and triamcinolone hexacetonide (TH) causes synovial atrophy and leads to significant clinical improvement when compared with others GCs. The drug is particularly safe even when performed in children. On the other hand, all the controlled studies published so far have not compared its intraarticular use to the systemic administration for the management of mono or oligoarticular flares (8, 18-24, 32, 39).

Recent work has reported that intraarticular glucocorticoids is safe to the cartilage and bone markers and confirmed that the procedure is effective to reduce synovitis and articular edema assessed by magnetic resonance imaging (40, 41).

Although the efficacy of intraarticular glucocorticoids is well documented, some studies question whether part of the therapeutical response may be related to its systemic absorption. The question is rather pertinent since improvement in long-distance joints has been observed after injection. Moreover, the drug can be detected in the plasma a few hours following intraarticular injection (33, 34, 42). The systemic effect is particularly common in procedures using soluble glucocorticoids. Reductions in cortisol and ACTH plasma levels have been observed after intraarticular injection with glucocorticoid preparations even the less soluble TH (17, 33, 34, 42).

Systemic glucocorticoid use in RA is also advocated to have DMARD-like effects. However, taken into consideration the great range of side effects including bone fragility and cardiovascular risk, systemic prolonged glucocorticoid use does not seem to be justified in the current management of RA (43-45).

Previous work from our group has demonstrated that intraarticular and intramuscular glucocorticoids equally suppress the hypothalamus-hypophysis-adrenal axis in the short term (46). On the other hand, the recovery from suppression seems to be faster when the intraarticular administration is used (46).

It is believed that the local atrophying effects on the synovial cells is superior and long lasting when compared to the systemic effect of glucocorticoid drugs. In contrast, adverse effects seem to be less important or significant when the drug is given by intraarticular injection (18, 32, 40, 42).

Table IV. Therapeutic responses according to ACR criteria (ACR 20, 50 and 70%) in patients with knee synovitis undergoing glucocorticoid intervention.

Time points (weeks)	IAI (n=30)	IM (n=30)	p^*
	ACR 20%		
T1	20% (6)	36.67% (11)	0.25
T4	20% (6)	36.67% (11)	0.25
T8	16.67% (5)	10% (3)	0.71
T12	13.33% (4)	23.33% (7)	0.51
	ACR 50%		
T1	10% (3)	3.33% (1)	0.61
T4	6.67% (2)	6.67% (2)	1.00
T8	0%	6.67% (2)	0.49
T12	3.33% (1)	6.67% (2)	1.00
	ACR 70%		
T1	0%	3.33% (1)	1.00
T4	0%	0%	1.00
T8	0%	0%	1.00
T12	0%	0%	1.00

(n); IAI: intraarticular injection group; IM: intramuscular injection group; *Fisher's exact test.

In the present study we chose to use TH for intraarticular use because it is the most effective glucocorticoid for that purpose and has the most delayed clearance from the synovial space (5, 17, 19-21). According to Derendorf *et al*., the TH intraarticular half-life is about 6 days, while the triamcinolone acetonide (TA) and betamethasone (BM) is 4.3 and 2.8 days, respectively. The systemic absorption percentage of these drugs after 3 days of a single intraarticular injection was 35-40% TH, 58-67% TA e 78% BM (17).

Since triamcinolone hexacetonide cannot be used by intramuscular administration, at the same dose administrated for the knee, an equivalent drug, TA, was used by intramuscular injection to mimic transient use of glucocorticoids, a common practice to control articular flares in RA, allowing a fixed dose of glucocorticoids for the IM group. The effect of an intramuscular injection of TA is about 1 to 6 weeks, the plasmatic and tecidual half-life is 2 -5 and 18-36 hours, respectively (47-51).

Other commom glucocorticoids such as methylprednisolone and betamethasone were excluded for the intramuscular administration because of the structural difference with triamcinolone hexacetonide. It remains unknown whether the results of this study would be different if we had used another glucocorticoid or another pathway such as oral or endovenous administration in the control group.

Despite the dose of TH (60mg) and TA (60mg) used in this study, there is no previous evidence, in current literature, of which dose is more suitable for intraarticular injection of the knee. In earlier studies the dose varies from 20 to 40mg of TH, our choice was based in the presence of synovitis in the rheumatoid knee and the aim of chemical synovectomy with this procedure (32, 41).

No previous study has compared the efficacy and safety of intraarticular and intra-muscular glucocorticoids for the treatment of monoarticular flares in RA patients. One study has compared the use of subacromial triamcinolone and systemic non-steroidal antiinflammatory drug (sodium diclofenac) for the management of the rotator cuff tendinitis. Both strategies were superior to placebo and hexacetonide injection was better than sodium diclofenac leading to better function and range of motion and significant pain reduction (52).

The most important outcomes in the present study are the variables associated with articular inflammation (pain, edema, morning stiffness). For all these outcomes, statistical analysis demonstrated that intraarticular injection was superior to systemic administration. Subjective improvement after intervention was measured by improvement percentage for the knee by the patient and also by a Likert's scale of improvement (by both patient and physician).

Table V. Likert's scale of improvement (LSI) scores according to the patient and the physician in patients with knee synovitis undergoing glucocorticoid intervention during the course of the study.

	Much better			Little better			Unchanged			Little worse			Much worse		
Group	IAI	IM	p^*	IAI	IM	p^*	IAI	IM	p^*	IAI	IM	p^*	IAI	IM	p^*
							According to the patient								
T1	24	17	0.09	4	11	0.07	2	0	0.47	0	2	0.47	0	0	1.0
T4	24	18	0.15	5	8	0.53	1	3	0.60	0	1	1.00	0	0	1.0
T8	27	16	**0.004**	3	7	0.29	0	4	0.12	0	0	1.00	0	3	0.23
T12	27	14	**<0.001**	2	11	**0.01**	1	1	0.47	1	1	0.47	0	2	0.47
							According to the physician								
T1	17	13	0.43	10	13	0.59	3	3	0.66	0	1	1.0	0	0	1.0
T4	19	11	0.07	10	17	0.11	1	1	0.47	0	1	1.0	0	0	1.0
T8	21	10	**0.01**	9	14	0.28	0	6	**0.03**	0	0	1.0	0	0	1.0
T12	19	6	**0.002**	9	14	0.28	1	8	**0.03**	1	2	1.0	0	0	1.0

IAI: intraarticular injection group; IM: intra-muscular injection group; * Fisher's exact test; T1: one week after intervention; T4: four weeks after intervention; T8: eight weeks after intervention; T12: 12 weeks after intervention.

In these parameters improvement was significantly higher in the IAI group as compared to IM group.

No significant difference between groups was observed for blood pressure, adverse effects and events. ACR20, ACR50 and ACR70% improvement criteria did not differ between groups along the course of the study probably reflecting to the low dosis of glucocorticoids used for intervention.

The fact that polyarticular glucocorticoid injection is superior to systemic administration was first suggested by open studies by McCarty *et al*. in 1995 and 1972 (18, 32) using triamcinolone hexacetonide and more recently by Proudman *et al*. (2000) using methylprednisolone (36). Previous work from our group has found that polyarticular glucocorticoid injection using triamcinolone is superior to its intramuscular use in RA patients. At both medium (ACTH plasma levels, lower painful joint count, systemic adverse effects and disease activity according to the patient) and short terms (ACR20, ACR50 and ACR70% improvement criteria), polyarticular injection with triamcinolone was superior to its systemic intramuscular administration. In that work, it is possible that patients in the intramuscular group have been favored by the minipulsetherapy effect caused by the high dose of triamcinolone used (46).

Polyarticular injection with glucocorticoid is in agreement with the more aggressive therapeutic approach for patients with RA. However, the procedure is not performed routinely by most the rheumatologists. Conversely, monoarticular glucocorticoid injection is frequently used by rheumatologists in their daily practice in spite of the lack of controlled studies evaluating the matter. In the present study we intended to compare the efficacy of glucocorticoids when given by intraarticular or systemic administration. Choosing the present population had the main purpose of selecting groups where the only difference would be the administration pathway of a small doses of glucocorticoids, with reduced potential for contamination or co-intervention.

The presence of persistent monoarticular synovitis is rather common in patients with RA after treatment with DMARDs or biological agents. In this case, the question is posed to the clinician whether to use intraarticular glucocorticoids or to transiently increase its systemic dosis. This study demonstrates that intraarticular glucocorticoids for the treament of knee synovitis is superior to its systemic administration.

The intraarticular approach led to significant improvement of the local signs and symptoms with minimum side effects. We believe that even in the new era of biological agents, local, fast and low cost interventions should not be forgotten as an important tool to manage pauciarticular manifestations in RA patients.

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