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CLINICAL RESEARCH

Adding Triamcinolone Improves Viscosupplementation: A Randomized Clinical Trial

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Abstract

Background Intraarticular injections, mainly using long-lasting corticosteroid suspensions, have long been used to treat knee osteoarthritis. Viscosupplementation is a relatively new approach with injection of a variety of agents. When comparing viscosupplementation with intraarticular injections of corticosteroids from baseline to the fourth week, steroids have been more effective for pain relief. By the fourth week they provide similar relief, but beyond that viscosupplementation appears to provide greater pain reduction. The delayed onset of symptomatic improvement combined with reports of reactive synovitis may discourage physicians and patients.

Questions/Purposes We therefore addressed three questions: Does the addition of triamcinolone to viscosupplementation (1) improve first-week pain and function compared with viscosupplementation alone, (2) diminish adverse effects of viscosupplementation alone, and (3) alter 6-month pain and function of viscosupplementation alone?

Methods We prospectively enrolled 104 patients with knee osteoarthritis and randomized them to receive either a single intraarticular injection (6 mL) of hylan GF-20 (Group viscosupplementation [Group VS]), or a single intraarticular injection of hylan GF-20 (6 mL) and 1 mL (20 mg) of triamcinolone hexacetonide (Group VS + T). VAS, WOMAC^{TM}, and Lequesne questionnaires were completed at baseline and at Weeks 1, 4, 12, and 24.

Results At Week 1 the WOMAC and VAS scores were lower in Group VS + T, compared with Group VS. There was no difference regarding the adverse effects. At Weeks 4, 12, and 24 there were no differences in the groups.

Conclusions The addition of triamcinolone hexacetonide improves first-week symptom and functional scores of viscosupplementation, but not beyond. It does not seem to increase the likelihood of adverse effects.

Level of Evidence Level I, therapeutic study. See Guidelines for Authors for a complete description of levels of evidence.

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Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

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Introduction

Intraarticular injections have been used for many years to treat arthritis and other painful articular disorders, mainly using long-lasting crystalline corticosteroid suspensions [16]. Viscosupplementation is a relatively new intervention that is now widely used and recommended for the treatment of knee osteoarthritis (OA) [3, 7, 11, 21, 31]. It is comprised of the injection of exogenous hyaluronic acid (HA) in diarthrodial joints. HA is a polysaccharide, naturally produced by B synoviocytes of the synovial membrane, and its

high-weight molecules contribute to form a high-viscosity solution, which serves as a lubricant and shock absorber [2, 25], among other functions. Viscosupplementation reportedly relieves pain [13] but it also is considered a disease-modifying OA drug [14, 29] with benefits that have been observed in a period of 6 months to 2 years [22]. It is believed that the long-term effectiveness of HA is attributable to its modulating action in the inflammatory process that occurs in the osteoarthritic joint and in its interaction with the CD44 synoviocytes receptors [28, 30].

Clinical trials [8, 29] and meta-analyses [3, 7, 11] have documented improvement in pain and function with viscosupplementation. Several placebo-controlled studies [4, 7, 11] showed an improvement began only within 2 to 5 weeks after the procedures. When comparing viscosupplementation with intraarticular injection of corticosteroids, Bannuru et al. [4] suggested that from baseline to Week 4, intraarticular steroids were more effective for pain relief. By the fourth week, however, both provided similar relief, but beyond the eighth week, exogenous HA provided greater pain reduction. The mechanism of action of HA with delayed onset of pain and functional improvement, combined with reactive synovitis [12], may discourage some physicians and patients from commonly using this treatment.

We therefore addressed three questions: Does the addition of triamcinolone to viscosupplementation (1) improve first-week pain and function compared with viscosupplementation alone, (2) diminish adverse effects of viscosupplementation alone, and (3) alter 6-month pain and function of viscosupplementation alone?

Patients and Methods

This prospective, double-blind parallel, group-controlled trial was conducted under the principles of the Helsinki Declaration and approved by the Ethics Committee for the Analysis of Research Projects (CAPPesq) under protocol number 0073/10. To meet the eligibility requirements, a patient had to have: (1) met the American College of Rheumatology criteria for knee OA [1]; (2) no previous fractures of the index knee; (3) no previous surgeries on the index knee; (4) no allergies to any of the substances used; (5) no rheumatoid arthritis; (6) no intraarticular injection in the index knee in the past 6 months; (7) been receiving usual care for OA for at least 6 months; and (8) been able to understand and agree with the informed consent. The exclusion criteria included: (1) undergoing surgery during the study; (2) receiving an intraarticular injection during the study; (3) having a severe reaction to the procedure; and (4) having an articular infection of the index joint develop during the study.

At the time of the study there were approximately 250 patients being treated for knee OA at the Osteometabolic Diseases Group at the University of São Paulo Medical Center (Fig. 1). All patients in our department receive the same treatment protocol, which we call usual care for knee OA. Usual care consists of patient education through lectures, handouts, audiovisual material, and guidance given by orthopaedic surgeons, nutritionists, psychologists, occupational therapists, physical therapists, physical educators, and social workers. All patients, except those with

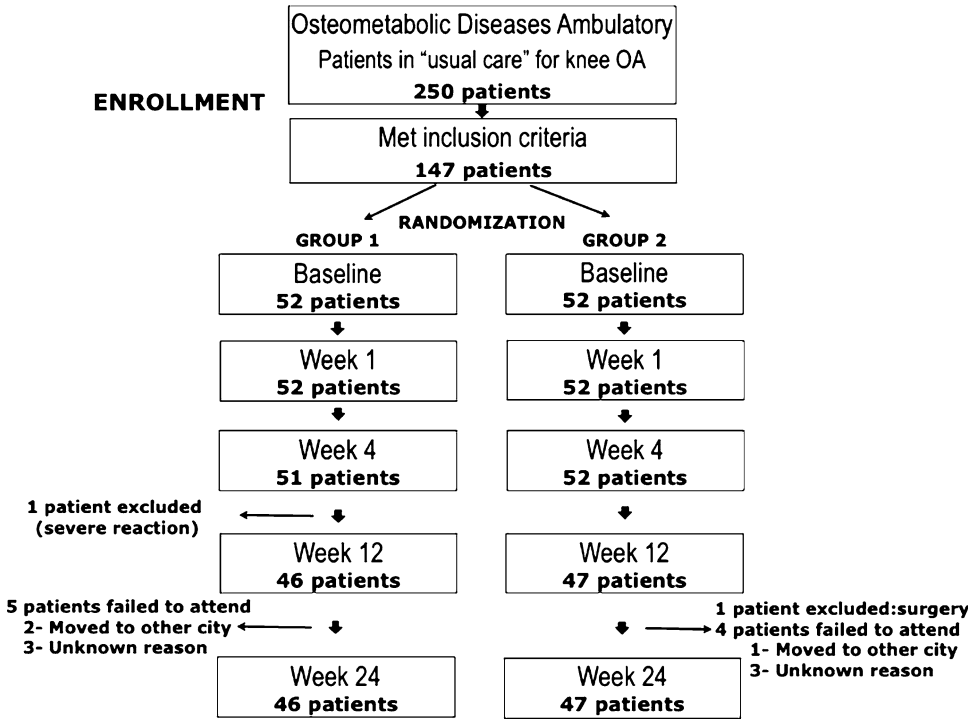

Fig. 1 The flow of our study is shown in this diagram.

Table 1. Nominal characteristics by groups

Variable	Group VS		Group VS + T		Total		p value
	Number	%	Number	%	Number	%	
Gender							0.819
Male	13	25	12	23	25	24	
Female	39	75	40	77	79	76	
Race							0.823*
Asian	1	2	1	2	2	2	
White	33	63	36	69	69	66	
Black	4	8	5	10	9	9	
Mixed	14	27	10	19	24	23	
Kellgren & Lawrence grade [18]							0.969
1	7	13	6	11	13	12	
2	14	27	16	31	30	29	
3	18	35	18	35	36	35	
4	13	25	12	23	25	24	

VS = viscosupplementation; VS + T = viscosupplementation plus triamcinolone; all p values were calculated using the chi-square test except for * which is a likelihood ratio.

contraindications, take analgesics (on demand), such as paracetamol and codeine. According to the knee alignment, we also may recommend insoles. We do not routinely give NSAIDs to our patients. Of the approximately 250 patients, 147 met the eligibility criteria for our study, and 104 were randomly selected with a computer-generated program. All invited patients agreed to participate. Patients were recruited between January 2011 and March 2011. All patients were evaluated clinically and received intraarticular injections between March 2011 and April 2011. The trial ended by October 2011, Week 24 of the followup.

One week before the procedure, patients who met the eligibility criteria responded to VAS, WOMAC™ [5], and Lequesne questionnaires [20]. Anthropometric data also were collected, such as age, gender, race, height, weight, and BMI. All patients had plain radiographs of their knees including AP with unilateral weightbearing, lateral, and patellar axial views). Three of us (GCC, AFP, RF) examined all radiographs to classify the severity of OA using the Kellgren and Lawrence scheme [18]. In 34 cases there was interobserver disagreement. In all those cases, we considered the level of classification given by the majority (two observers). None of the radiographs resulted in total discordance (three different classifications).

Patients were randomly divided into two groups of 52 patients. Randomization was performed by a computer-generated program (available at: http://www.randomization.com/). Group viscosupplementation (Group VS) received a single intraarticular injection of 6 mL of hylan GF-20 (FDA-approved). The group with viscosupplementation and triamcinolone (Group VS + T) received an intraarticular injection of 6 mL of hylan GF-20 and 1 mL (20 mg) triamcinolone hexacetonide (FDA approved). The sample size was estimated by calculating a number to allow statistical power of 80% and a significance level of 5%. Bannuru et al. [4] found, 2 weeks after injection, an effect size of 0.39 favoring corticosteroid alone versus viscosupplementation. To be able to detect a difference of at least 25% in groups, we established the value of 10 for the difference to be detected, which is a value commonly used for studies using VAS and WOMAC™. Considering the SDs reported in a previous study [23] and an estimation of 20% of dropouts and exclusions, we calculated 52 patients per group. The investigator (MUR) who gave the questionnaires was blinded (unaware of the patient's group and did not perform any injections).

To determine if the groups differed with respect to the nominal variables (gender, race, and Kellgren and Lawrence grade), we used absolute and relative frequencies, and checked for association with chi-square or Fisher exact tests when the likelihood ratio sample was insufficient to use the chi-square test. The quantitative characteristics were described as groups with the use of summary measures (mean, SD, median, minimum, maximum), and the groups were compared using Student's t-test. There were no differences between the groups in nominal (Table 1) and numeric characteristics (Table 2).

All procedures were performed in an outpatient setting with the patients receiving local anesthesia. The joint punctures were performed by three orthopaedic surgeons (GCC, AFP, RF) who had experience in viscosupplementation. If present, knee effusion was extracted before the injection. Patients were blinded (blocked from watching the procedures by the use of a windscreen sunshade and did not know to which group they were assigned). Patients with

Table 2. Numeric characteristics by groups

Variable	Group	Mean	SD	CI (95%)		Number	p value
				Minimum	Maximum		
Age (years)	VS	61	12	57	64	52	0.062
	VS + T	65	9	62	67	52	
Weight (kg)	VS	80	15	76	84	52	0.136
	VS + T	76	11	73	79	52	
Height (m)	VS	1.63	0.09	1.60	1.65	52	0.773
	VS + T	1.62	0.08	1.60	1.64	52	
BMI (kg/m^2)	VS	30	5.24	29	32	52	0.157
	VS + T	29	4.08	28	30	52	

VS = viscosupplementation; VS + T = viscosupplementation plus triamcinolone; calculation of p values was done using the chi-square test.

Table 3. Score results by groups and moments

Variable		Group VS				Group VS + T			
Score	Moment	Mean	SD	CI (95%)		Mean	SD	CI (95%)	
				Inferior	Superior			Inferior	Superior
WOMAC™	Prestudy	50	16	46	55	55	18	50	60
	Week 1	46	19	41	51	34	20	29	40
	Week 4	39	18	34	44	32	18	27	37
	Week 12	34	19	29	40	36	16	32	41
	Week 24	37	19	31	42	38	17	33	43
VAS	Prestudy	67	20	62	73	70	24	64	77
	Week 1	55	27	48	63	39	25	32	45
	Week 4	50	24	44	57	37	25	30	44
	Week 12	46	26	39	54	46	24	40	54
	Week 24	49	22	43	56	50	23	43	57
Lequesne [20]	Prestudy	13	3.8	12	14	14	4.1	13	15
	Week 1	12	4	11	13	11	4.7	9.6	12
	Week 4	11	4.1	10	12	9.7	4.1	8.5	11
	Week 12	10	4	8.5	11	11	3.7	9.7	12
	Week 24	10	4.2	9	12	11	3.7	10	13

VS = viscosupplementation; VS + T = viscosupplementation plus triamcinolone.

bilateral disease had both knees treated with the same drug, but only one knee (reported by the patient as the worst) was included in the study. All patients were discharged immediately after the procedures without any restrictions and with a prescription of 500 mg paracetamol that was to be administered every 6 hours for 3 days. All patients continued to receive usual care. The use of NSAIDs was forbidden.

The VAS, WOMAC™, and Lequesne questionnaires were given again at the scheduled visits at Weeks 1, 4, 12, and 24. The primary outcomes were improvements in knee pain and function, as expressed by the results of the questionnaires. Secondary outcomes were the presence of adverse effects (knee pain, effusion, or erythema at Week 1), and any correlation between the anthropometric data and the clinical outcomes.

The pain and functionality scales were described according to groups and times of assessments using summary measures. We compared the values between groups at each followup using ANOVA, followed by Tukey's multiple comparison, to compare groups and followups, two by two.

Results

Baseline scores were similar ($p = 0.062$ to $p = 0.969$) between the groups. At Week 1, Group VS + T showed improvement in all the scores (Table 3), with a difference

from baseline. Group VS showed mild improvement at Week 1 (Table 3), with a difference from baseline ($p = 0.009$) only in VAS. Comparing the two groups, Group VS + T showed lower levels in WOMAC™ ($p = 0.038$) and VAS ($p = 0.014$) at Week 1.

Seventeen percent of all patients reported knee pain or discomfort and 4.8% had joint effusions after the injections. There were no differences between the groups (Table 4). One patient in Group VS presented with severe effusion and pain at Week 1 and was treated with arthrocentesis and an intraarticular corticosteroid injection. This patient was excluded from the study. All other cases of adverse events were mild, and the symptoms were relieved with ice, rest, and analgesics.

During the followup, the difference between the groups decreased and at Weeks 4, 12, and 24 there were no differences between the groups in any score. At 6 months followup, both groups showed similar values in WOMAC™ ($p > 0.999$), VAS ($p > 0.999$), and Lequesne index ($p = 0.942$).

Table 4. Adverse effects

Adverse effects	Group VS		Group VS + T		Total		p value
	Number	%	Number	%	Number	%	
Pain							
–	44	86	41	79	86	83	0.300
+	8	14	11	21	18	17	
Effusion							
–	49	94	50	96	99	95	> 0.999*
+	3	6	2	4	5	5	

VS = viscosupplementation; VS + T = viscosupplementation plus triamcinolone; chi-square test was used to calculate p values except for * which was calculated using Fisher's exact test.

Discussion

Viscosupplementation remains a controversial OA treatment option, especially because of the delayed onset of pain and functional improvement. Adding corticosteroids to the procedure could speed the relief of symptoms owing to its fast mechanism of action. We therefore addressed three questions: Does the addition of triamcinolone to viscosupplementation (1) improve first-week pain and function compared with viscosupplementation alone, (2) diminish adverse effects of viscosupplementation alone, and (3) alter 6-month pain and function of viscosupplementation alone?

Our study had some limitations. First, we did not limit the use of analgesics or any other nonpharmacologic treatment. We believe that viscosupplementation is a procedure that should not exclude any other type of treatment for OA, therefore, patients received usual care but were asked to keep track of the use of analgesics, with no differences between groups. Second, clinical scores, such as the WOMAC™ and Lequesne, cannot distinguish one knee from another when the patient has bilateral OA. Therefore, patients with bilateral disease had both knees treated with the same drug and only the knee reported as the worst by the patient was considered and classified with the Kellgren and Lawrence grade. Third, we had no saline injection placebo group. Several studies [3, 7, 8, 11, 22] have compared viscosupplementation versus placebo and intraarticular corticosteroid versus placebo [6, 15, 26] (Table 5). We also were able to have a control group that received treatment (VS), conducting a study without the ethical issues of using a placebo group. Fourth, most of the HA products are supposed to be administered three to five times on a weekly injection basis. The regimen adopted for this study was a single injection of 6 mL of hylan GF-20, which is accepted only for this particular product [8]. Fifth, there was concern regarding the chondrotoxicity of

Table 5. Comparison of the literature

Study	Comparison	Followup		
		< 4 weeks	4–12 weeks	> 12 weeks
Bannuru et al. [3]*	VS versus placebo	0.31	0.46	0.21
Bannuru et al. [4]*	VS versus steroid	−0.39	−0.01	0.22
Bellamy et al. [6]$	Steroid versus placebo	21.91	7.10 #	7.30 #
Bellamy et al. [7]$	VS versus placebo	12.54+	22.46+	20.70+
Divine et al. [11] $	VS versus placebo	5.4 #	10.4	11.0
Current study&	VS + T versus VS	16.77	12.83	−0.46 #

VS = viscosupplementation; VS + T = viscosupplementation plus triamcinolone; * results expressed as effect size. Positive result favors viscosupplementation and a negative result favors control group; $ results expressed as weighted mean difference (VAS decrease in Group VS/steroid minus VAS decrease in placebo group); &mean difference (VAS decrease in Group VS + T minus VAS decrease in Group VS); +pain on weightbearing; # no statistically significant differences detected.

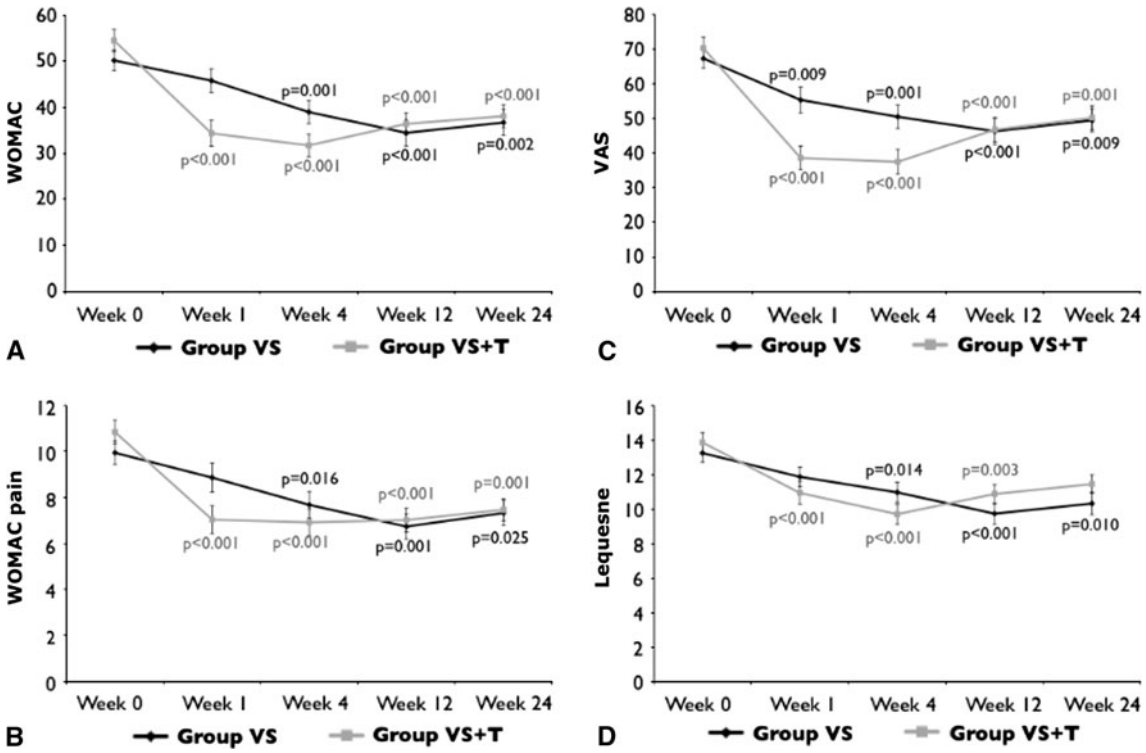

Fig. 2A–D The graphs show the mean results with respective standard errors for (**A**) WOMAC™, (**B**) WOMAC™ pain subscale, (**C**) VAS, and (**D**) Lequesne index. At Week 1, there are differences in WOMAC™ (p = 0.038) and VAS (p = 0.014) favoring Group VS + T. P values on the graph relate only to differences between the scores at followup and baseline, not differences in scores between the groups.

intraarticular corticosteroid injections [24], but after a review of the literature [6, 15] we concluded there was enough safety evidence on this matter. One 2-year followup randomized clinical trial showed no loss of joint space width after the intraarticular injection of triamcinolone hexacetonide at 3-month intervals [26]. Sixth, no objective methods were performed to evaluate disease progression, such as joint space width [27] or MRI [9, 17]. It would bring complexity and the necessity of a longer followup.

We observed improvement in all patients, but the VAS and WOMAC™ scores decreased to lower levels and sooner in Group VS + T. This phenomenon can be explained by the faster pain relief and function improvement for intraarticular corticosteroid injections [4, 6, 15]. The charts (Fig. 2) showed two different curve patterns for each group until Week 4, probably owing to the effect of the corticosteroid. Group VS showed a smoother curve, denoting the more modulating mechanism of action of the HA.

Adverse events, such as knee effusion, pain, heat, and erythema, may occur in approximately 4.2% of the patients [19]. HA injections also may lead to an acute arthritis [12] owing to an allergic reaction or foreign body reaction. The addition of triamcinolone should reduce the frequency and severity of such reactions. In our study, one patient from Group VS had a severe reaction. Both groups had a higher rate of pain and similar rate of effusions, as seen in the literature (ranging from 0.1% to 8.1% [3, 7, 19]). However, there was no difference between the groups regarding adverse events. Since the pseudoseptic reaction is a rare event [12], it might be necessary to have a larger number of patients to reach any conclusion on that matter.

We found no differences in WOMAC™, VAS, and Lequesne values at 6 months' followup. Despite the similar clinical outcomes, we do not know whether the addition of steroids will affect the disease modification effect of the HA. The osteoarthritic chondrocytes are deficient in glucocorticoid receptors, and a poor response to circulating steroids may be one of the factors involved with the higher levels of cytokines and metalloproteinases in an osteoarthritic joint [10]. Therefore, in addition to improving first-week pain and function scores of viscosupplementation, one can speculate that triamcinolone could positively affect the action in disease progression. More studies are needed on this matter. Regarding the type of HA used for viscosupplementation, there is no convincing evidence of one product being superior over another regarding molecular weight, concentration, or the number of crosslinks [3, 11]. We believe that our results can be extrapolated to the viscosupplementation procedure in general.

The addition of 1 mL of triamcinolone hexacetonide improved the first-week symptom and functional scores of viscosupplementation, and it did not alter its adverse effects or the 6-month symptom and functional improvement.

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