RAPID COMMUNICATION

Adding triamcinolone to viscosupplementation: one year outcome of randomized trial

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OBJECTIVE: This is an extended follow-up of a randomized controlled trial to evaluate if the addition of triamcinolone to viscosupplementation could alter one-year pain and function of viscosupplementation alone. This is a Level I Therapeutic study (See Guidelines for Authors for a complete description of levels of evidence).

METHODS: In a previously reported study we prospectively enrolled 104 patients with knee osteoarthritis and randomized them to receive either a single intra-articular injection (6 mL) of hylan GF-20 (Group viscosupplementation [Group VS]), or a single intra-articular injection of hylan GF-20 (6 mL) and 1 mL (20 mg) of triamcinolone hexacetonide (Group VS + T). Visual Analogue Scale, WOMAC™, and Lequesne questionnaires were completed at baseline, at weeks 1, 4, 12, 24. At the one-year follow-up point, all patients were recruited and reassessed.

RESULTS: At one year, the effects of treatment observed in the previous periods were present, with no differences between groups; only the Group receiving hylan + triamcinolone hexacetonide still showed a difference from baseline in the Visual Analogue Scale questionnaire.

CONCLUSIONS: The addition of triamcinolone hexacetonide improves first-week symptoms and functional scores of viscosupplementation and does not alter its adverse effects. There might be benefits for the one-year pain results.

KEYWORDS: viscosupplementation; osteoarthritis; intraarticular injection; triamcinolone.

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INTRODUCTION

Viscosupplementation, namely the injection of exogenous hyaluronic acid into diarthrodial joints, though widely used and recommended for the treatment of knee osteoarthritis (OA),[1–5] still raises controversy, especially regarding its long-term results. In contrast to the fast pain-relieving action of intra-articular injection of corticosteroid,[6,7] viscosupplementation reportedly relieves pain[8] but it is also considered an osteoarthritis disease-modifying drug[9–11] with benefits that have been observed during a period of 6 months to 2 years.[12] In a previous study,[13] we found that the addition of 1 mL of triamcinolone hexacetonide improved the first-week symptom and functional scores of viscosupplementation, and did not alter its adverse effects (such as knee pain, effusion or eritema at week one attendance) nor the 6-month symptom and functional improvement. There are still doubts regarding the influence of the addition of corticosteroids on the longer term outcomes of viscosupplementation. We present here the one-year patient-reported outcomes in an extended follow-up of this randomized controlled trial.

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PATIENTS AND METHODS

This is an extended follow-up of a prospective, double-blind parallel, group-controlled trial that was approved by the institutional Ethics Committee for the analysis of research projects (CAPPesq) under the protocol number 0073/10.[13] We recruited all the patients that had participated and eighty-seven patients attended the one-year follow-up.

The same blinded investigator - MUR - (still unaware of the patient's group) administered the Visual Analogue Scale, WOMAC™, and Lequesne questionnaires at the scheduled visit, after one year. The envisaged primary outcomes were improvements in knee pain and function, as expressed by the results of the questionnaires. Envisaged secondary outcomes were 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 (mean, standard deviation, median, minimum, maximum). We compared the values between groups at each follow-up using ANOVA, followed by Tukey's multiple comparison, to compare groups and follow-ups, two by two.

RESULTS

Figure 1 shows the study's flow diagram. Eighty-seven patients were included in the final analysis (dropout rate of 16.8%). As demonstrated in Figs. 2, 3 and 4, during the follow-up, the difference between the groups decreased and at Weeks 4, 12, 24; at one year there were no differences between the groups in any score.

Table 1 contains the main results according to groups and specific moments. At the one-year follow-up, both groups showed similar values in WOMAC™ ($p > 0.999$), and both groups were still better than baseline ($p < 0.001$ and $p = 0.015$ respectively). The Lequesne index showed similar values for both groups ($p = 0.942$) and none of them were better than baseline ($p > 0.05$). The Visual Analogue Scale also showed similar values for both groups ($p = 0.984$) at one-year follow-up, but Group VS + T still showed a difference from baseline ($p < 0.001$), while Group VS no longer did ($p = 0.304$).

DISCUSSION

In our previous study we found that adding corticosteroids to viscosupplementation accelerated the relief of symptoms owing to its fast mechanism of action.[13] There is no consensus, however, whether the addition of steroids will affect the disease-modifying effect of the hyaluronic acid. After one year in this randomized controlled trial, we found no statistically significant differences in pain and function between patients assigned to viscosupplementation alone and those assigned to viscosupplementation plus triamcinolone. However, only those assigned to VS + T group maintained better results with a difference from baseline for the Visual Analogue Scale.

We maintained our policy of not limiting the use of analgesics or any other nonpharmacologic treatment. Patients received usual care but were asked to keep track of the use of analgesics; no differences were observed between groups regarding the use of analgesics. No objective

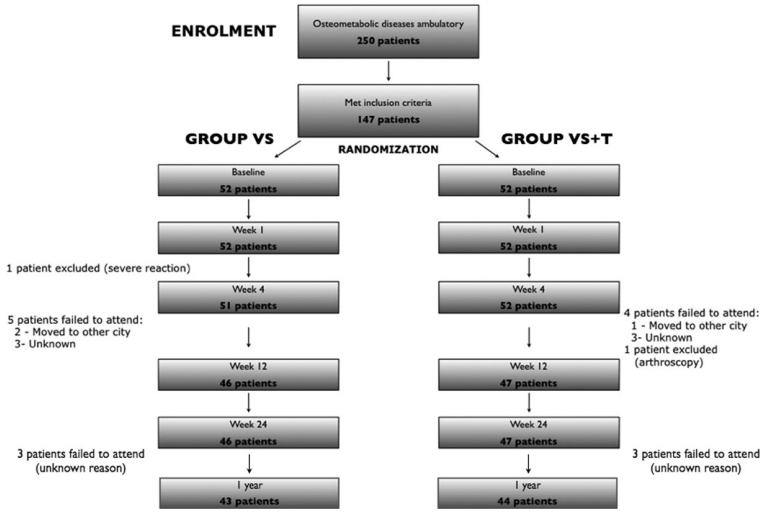

Figure 1 - Flow diagram for the follow-up of patients.

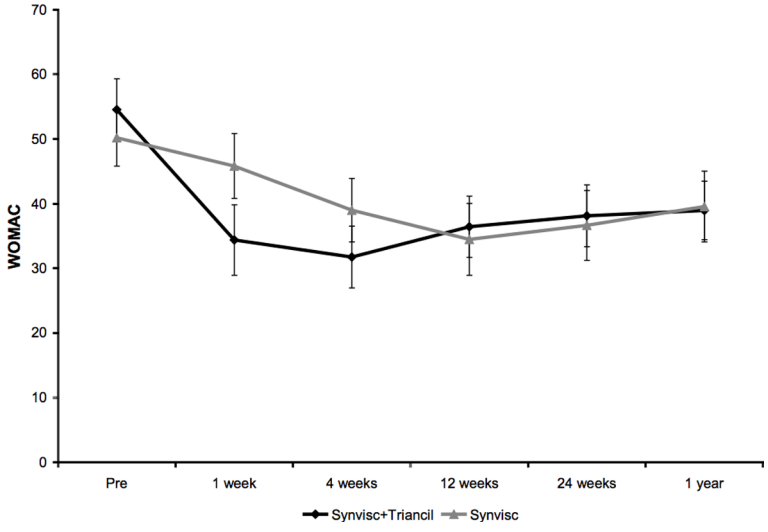

Figure 2 - Mean results and respective confidence intervals of WOMAC according to groups over time.

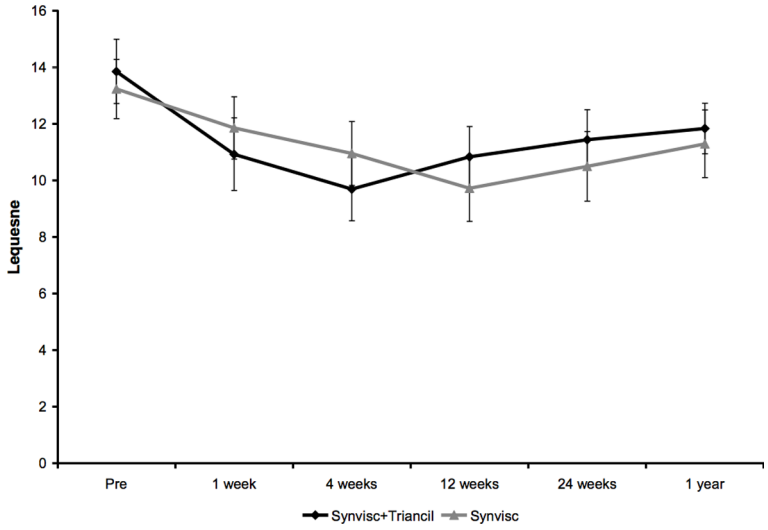

Figure 3 - Mean results and respective confidence intervals of Lequesne according to groups over time.

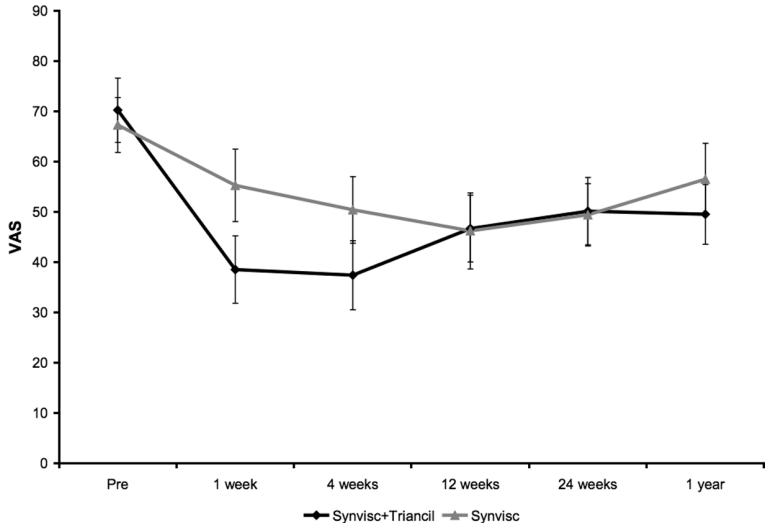

Figure 4 - Mean results and respective confidence intervals of VAS according to groups over time.

methods were performed to evaluate disease progression, such as joint space width or MRI.[14] Because the study was originally designed for a 6-month follow-up, and because this was considered a short period for such analysis, we extended the duration of the follow-up. After one year we could have used an objective method to analyze disease modification, but unfortunately our data only included clinical outcomes. Another concern was whether corticosteroids could break the cross-links of the hylan molecules, jeopardizing the product's effect. We performed a review of the literature and found no information on that matter. We did not repeat the courses of hyaluronic acid or triamcinolone. There is no established consensus regarding the optimal dosing regimen for the intra-articular treatment of osteoarthritis.[15] Current recommendations for dosing interval appear to have arisen as a consequence of a misinterpretation of previously published works, and practitioners should individually tailor their selection of agent and dosing regimen to patient needs and clinical response.[15]

At one year, we still observed improvement in all patients. As seen in our previous study, the Visual Analogue Scale and WOMAC™ scores decreased sooner and to lower levels in Group VS + T, a phenomenon that can be explained by the faster pain relief and function improvement for intra-articular corticosteroid injections.[6,7,16] We found no differences in WOMAC™, Visual Analogue Scale, and Lequesne values at one-year follow-up. However, at one year, patients that received triamcinolone still had better results on the Visual Analogue Scale compared to the baseline, unlike the group that did not receive triamcinolone. A possible explanation for this finding is the important role played by glucocorticoids in the pathogenesis of OA.[17] A recent study[18] found that lower estradiol concentration is a risk factor for knee OA and lower androstenedione concentration is a risk factor for hip OA in women. The findings suggest a role of circulating sex steroids in the pathogenesis of OA and that

Table 1 - Results obtained for according to groups (viscosupplementation alone VS or ciscosupplementation plus triamcinolone at specific moments of follow-up).

Moment of follow-up	Group VS + T			Group VS		
	Mean	SD	N	Mean	SD	N
WOMAC						
Pre	54.54	17.58	52	50.21	16.15	52
1 week	34.38	20.04	52	45.83	18.52	52
4 weeks	31.75	17.58	52	39.00	17.87	51
12 weeks	36.43	16.50	47	34.48	19.25	46
24 weeks	38.11	16.72	47	36.63	18.76	46
1 year	38.95	15.07	43	39.55	18.55	44
Lequesne						
Pre	13.86	4.18	52	13.24	3.85	52
1 week	10.93	4.73	52	11.86	4.05	52
4 weeks	9.70	4.12	52	10.96	4.13	51
12 weeks	10.84	3.76	47	9.73	4.06	46
24 weeks	11.45	3.70	47	10.50	4.26	46
1 year	11.84	3.00	43	11.30	4.04	44
VAS						
Pre	70.21	23.59	52	67.27	20.08	52
1 week	38.52	24.65	52	55.29	26.52	52
4 weeks	37.40	25.24	52	50.41	24.11	51
12 weeks	46.68	23.26	47	46.22	26.18	46
24 weeks	50.15	23.46	47	49.39	21.44	46
1 year	49.51	19.88	43	56.52	24.18	44

VS: hylan GF-20 (viscosupplementation); T: triamcinolone

modifying these steroid concentrations may provide potential strategies for the prevention and treatment of knee and hip OA. Dexamethasone has been shown to decrease joint inflammation and joint tissue degradation and was chondroprotective in a post-traumatic osteoarthritis animal model.[19] 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.[20] Therefore, in addition to improving first-week pain and function scores of viscosupplementation, triamcinolone could positively affect the action in disease progression, and the Visual Analogue Scale values of our extended follow-up corroborates that theory.

In conclusion, the addition of 1 mL of triamcinolone hexacetonide improved the first-week symptom and functional scores of viscosupplementation and did not alter its adverse effects. There might be benefits for one-year pain symptom improvement.

RESUMO

OBJETIVO: Este é o seguimento prolongado de um ensaio clínico randomizado para avaliar se a adição de triancinolona à viscosuplementação poderia alterar a dor e o efeito da viscosuplementação usada isoladamente, um ano após a aplicação terapêutica. Este é um estudo terapêutico Nível I.

MÉTODOS: Em um estudo relatado anteriormente, 104 pacientes foram prospectivamente incluídos. Os pacientes apresentavam osteoartrite do joelho e foram randomizados para receber uma única injeção intra-articular (6 mL) de hylan GF-20 (grupo viscosupplemenção) ou a mesma aplicação acrescida de 1 ml (20 mg) de hexacetonida de triancinolona. Foram preenchidos os questionários Escala Visual Analógica, WOMAC™ e Lequesne no início do estudo e nas semanas 1, 4, 12, 24 pós-tratamento. Ao fim de um ano de acompanhamento todos os pacientes foram recrutados e reavaliados.

RESULTADOS: Em um ano, os efeitos do tratamento observado nos períodos anteriores estavam presentes, sem diferenças entre os grupos; apenas o grupo que recebeu hylan + triancinolona hexacetonida ainda mostrou uma diferença em relação à linha de base no questionário Escala Visual Analógica.

CONCLUSÕES: A adição de hexacetonida de triancinolona melhora os sintomas e escores funcionais observados com viscosuplementação simples na primeira semana pós-tratamento e não altera os seus efeitos adversos. Pode haver benefícios para a dor após um ano.

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