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Original Article

Results evaluation of the use of intra-articular sodium hyaluronate in the post-operative knee arthroscopy☆,☆☆

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ABSTRACT

Objective: to evaluate the efficacy of hyaluronic acid in the post-operative of knee arthroscopy.
Methods: we have evaluated 49 patients undergoing arthroscopic procedure with the use of intra-articular hyaluronic acid (Group 1) and 49 patients undergoing arthroscopic procedure without the use of hyaluronic acid (Group 2). Patients were evaluated based on the Visual Analogue Scale, household analgesia, assessment of the Range of Motion with a goniometer, and the Lysholm questionnaire.
Results: there were no substantial adverse effects on either group.
Conclusion: the use of hyaluronic acid in the post-operative of knee arthroscopy is justified due/because it leads to a decrease in pain in the early stage, enabling faster recovery of the patient.

Avaliação dos resultados do uso do hialuronato de sódio intra-articular no pós-operatório da artroscopia do joelho

Palavras-chave:
Artroscopia
Joelho
Ácido hialurônico
Viscossuplementação

RESUMO

Objetivo: avaliar a eficácia do uso do ácido hialurônico no pós-operatório de artroscopia de joelho.
Métodos: foram avaliados 49 pacientes submetidos ao procedimento artroscópico associado ao uso do ácido hialurônico intra-articular (Grupo I) e 49 pacientes submetidos ao procedimento artroscópico sem uso do ácido hialurônico (Grupo II). Os pacientes foram avaliados com base na Escala Visual Analógica de dor (EVA), analgesia domiciliar, amplitude do movimento do joelho com goniômetro e no questionário Lysholm.
Resultados: não ocorreram efeitos adversos significativos em nenhum dos dois grupos.

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Conclusão: o uso do ácido hialurônico no pós-operatório de artroscopia de joelho é justificado por levar a uma diminuição da dor na fase inicial e possibilitar uma recuperação mais rápida do paciente.

Introduction

The use of intra-articular medication in the immediate post-operative period in the area of arthroscopic knee surgeries is controversial, with prospects for new behaviors and routines, and with authors for and against the use of hyaluronic acid post-operatively.[1,2]

A knee arthroscopy is a medical procedure more usual in the United States of America (USA), and is effective for symptom relief in patients with intra-articular loose bodies, chondral injury and meniscal pathology.[2]

The performance of human joints is strictly related to the viscoelastic properties of synovial fluid, which determines the strength transmission, lubrication and protection of articular cartilage. This viscoelasticity depends on the concentration of hyaluronic acid in the sinovial fluid.[3]

Other actions of hyaluronic acid would be an anti-inflammatory effect (decreased gene expression of cytokines, prostaglandin production, and intra-articular concentration of metalloproteinases) and analgesic (inhibition of nociceptors), stabilization of cartilaginous matrix, chondrocyte proliferation, increased production of type II collagen and its decreased degradation.[4–6]

Some authors believe that exogenous hyaluronic acid also stimulates the production of endogenous hyaluronic acid, which would explain its long-term effect.[7] With respect to the analgesic effect of intra-articular hyaluronic acid, it is believed that, initially, it would be smaller than the intra-articular corticosteroid injection, but with persistence for longer periods.[8]

Another source of debate is the discussion regarding the number of doses of hyaluronic acid to be effective, but there was no difference in the comparison between three and six doses at weekly intervals.[9]

Some authors claim that, during an arthroscopic knee surgery, a decrease in intra-articular hyaluronic acid concentration may occur and, as immediate therapy, recommend intra-articular applications of sodium hyaluronate 20 mg after surgery, and subsequently four injections at weekly intervals.[10]

The aim of this study was to compare the results of the use of intra-articular sodium hyaluronate in a group of patients undergoing arthroscopic surgery due to meniscal lesions *versus* results observed in a group of patients not treated by this complementary therapy.

Materials and methods

Ninety-eight patients with meniscal lesions were studied. These patients were treated from March to November 2005 by arthroscopic surgery with partial meniscectomy of the medial meniscus, always by the same surgical team.

Their ages ranged from 18 to 65 years (mean: 34 years). Sixty-five (63%) were men and 33 (37%), women.

The participants were randomly divided into two groups of 49. The first group was treated with intra-articular sodium hyaluronate 20 mg (Polireumim, TRB Pharma) in the immediate post-operative period and, subsequently, with a weekly application for four consecutive weeks. In the second group, this treatment was not done. The surgeon was unaware of the group to which each patient belonged, having been informed only after skin suture, at the time of completion (or not) of the infiltration (Table 1).

All patients were rehabilitated according to the same protocol, with evaluations after three, eight, 15, 30 and 60 days, and were instructed to return to sport practice after 60 days of surgery.

All patients underwent the same surgical technique, with the use of only two infrapatellar portals (medial and lateral) and, on average, with joint infusion (6 L of saline 0.9%), using an infusion pump at a mean pressure of 50 mmHg. All randomized patients showed no significant changes in cartilage and, in this study, only cases of Outerbridge grade I and II chondropathy (Table 1) were included.

All patients were anesthetized by subarachnoid block with bupivacaine 0.5% associated with glucose 12.5 to 15 mg, without opioids. A pneumatic tourniquet was also used, with an average time of 35 min.

After hospital discharge (mean: 12 h after the intervention), both groups were treated with cephalexin 500 mg PO 6/6 h for seven days and, in case of pain, dipyrone 50 drops to the limit of 6/6 h. The use of analgesics was controlled in a form, in which the patient had to check the date and time of use until the eighth day.

In Group 1, after skin suture the infiltrations were made in the lateral suprapatellar area, (once a week for four consecutive weeks). Besides the control on the form with the date and time of use of analgesics, patients underwent VAS. In all reviews, the range of motion of the knee was also measured with a goniometer; the Lysholm questionnaire was applied in the preoperatory on the day of surgery and on the 15th, 30th and 60th days post-operatively. All evaluations were performed by the same examiner who did not know at which group the patient belonged.

To avoid bias in the results because of the pain of infiltration, the assessments in the 8th, 15th and 30th days were always made before this procedure.

In the statistical analysis, analysis of variance with two factors and repeated measures on the time factor were made, assuming a first-order autoregressive correlation matrix between time points.[11] After the analysis, Tukey multiple comparisons were made[12] to see between which groups or time points occurred differences in scales.

The tests were performed with a significance level of 5%.

Table 1 – Characterization of sample.

Variables	n = 98	Group 1 = 49	Group 2 = 49
Age (years) – mean (SD)	34 (12.1)	36 (11.3)	33 (12.1)
Minimum–maximum	18–65	20–65	18–61
Gender – n (%)			
Female	33 (37)	15 (30.6)	18 (36.7)
Male	65 (63)	34 (69.4)	31 (63.3)
Operated site – n (%)			
Right	58 (59.2)	26 (53)	32 (65.3)
Left	40 (40.8)	23 (47)	17 (34.7)
Chondral lesion[a] *– n (%)*			
Without lesion	43 (43.9)	22 (44.9)	21 (42.9)
Grade I	31 (31.6)	14 (28.6)	17 (34.7)
Grade II	24 (24.5)	13 (26.5)	11 (22.4)

[a] Outerbridge.

Results

Considering the assessments by VAS, the results suggest more rapid reduction of pain in Group 1 *versus* Group 2. The analysis showed that the mean behavior of VAS was statistically different between groups over the evaluation time points ($p < 0.001$) (Fig. 1).

In comparing the different evaluation time points, the data in Table 2 show that both groups had a mean reduction in VAS with statistical significance at all evaluation time points, when compared to the previous time point ($p < 0.001$), but in the eighth and 15th days, Group 1 showed, on average, statistically lower VAS *versus* Group 2 ($p < 0.001$ and $p < 0.001$) and in other time points, there was no statistically significant difference in VAS between groups ($p > 0.05$) (Table 2).

With respect to the need for use of home analgesia, there was no statistical difference between the groups until the eighth day.

With regard to assessments made with the goniometer, it was observed that after 15 days the Group 1 had greater range of motion *versus* Group 2. After 30 days, this difference could still be observed, to a lesser extent, but without statistical significance. In the assessment made on the 60th day, the results were similar in both groups.

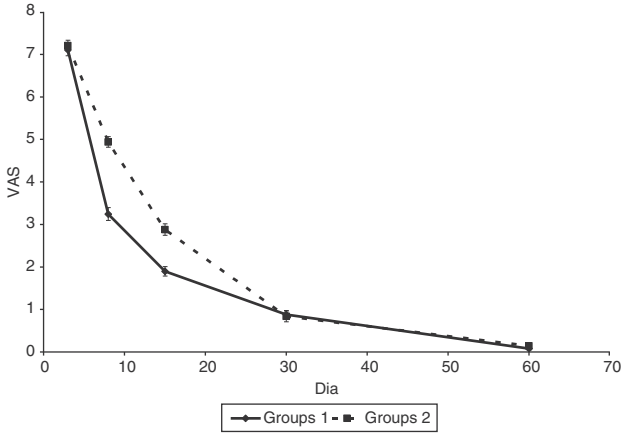

Fig. 1 – Graphical representation of the mean profiles and respective standard errors of VAS, according to groups.

In the evaluation with the Lysholm questionnaire (excellent: patients between 95 and 100 points, good: 94–84; regular: 83–65, and poor score: <64), we noted in the preoperative that the Groups 1 and 2 had an average of 46 and 48 points, respectively, classified then as poor (Table 3).

Table 3 shows that in both Groups (1 and 2), the mean Lysholm score decreased statistically from the preoperatory to 15 days post-operatively ($p = 0.003$ and $p < 0.001$, respectively), with "poor" rating in both groups. However, in the evaluation of the questions, we found that the largest difference between groups was observed in the items "pain" and "swelling", in which the Group 1 had better results *versus* Group 2. In other questions, the results were similar between groups.

In the 30th day the results showed the greatest statistical difference between groups. Group 1 averaged 90 points, classified as good, and Group 2 averaged 77 points, classified as regular. We perceived a greater difference in the questions about claudication, instability, swelling and squatting, and noticed that, just as that in the 15th day, the swelling was also an important factor.

At the last evaluation period, 60 days after the surgery, the two groups differed statistically, with 94 points in Group 1 and 90 points in Group 2, both classified as good. In this evaluation, we realized that the two groups differed primarily in the item "climbing stairs", but without statistical difference between values.

In the allocation of the results of the Lysholm et al. questionnaire on a graph, earlier improvement of function in Group 1 *versus* Group 2 was noted in all assessments ($p < 0.001$) (Fig. 2).

In this study, some complications occurred: eight patients in Group 1 reported a need for analgesia after infiltration. In six of these cases, two patients required only one dose of dipyrone 50 drops, and in two of them, two days of dipyrone 50 drops 8/8 h were required.

None of the patients had post-operative infections, joint stiffness, or scar changes.

Discussion

Hyaluronic acid is a natural polymer of glycosaminoglycan family. It is an important constituent of the extracellular

Table 2 – Result of multiple comparisons of VAS among groups and time points.

Group/time point	Comparison	Mean estimated difference	Standard error	t value	gL	p
Group 1	3 days–8 days	3.86	0.10	38.60	384	<0.001
	3 days–15 days	5.20	0.13	41.05	384	<0.001
	3 days–30 days	6.22	0.14	44.25	384	<0.001
	3 days–60 days	7.02	0.15	47.27	384	<0.001
	8 days–15 days	1.35	0.10	13.48	384	<0.001
	8 days–30 days	2.37	0.13	18.67	384	<0.001
	8 days–60 days	3.16	0.14	22.49	384	<0.001
	15 days–30 days	1.02	0.10	10.21	384	<0.001
	15 days–60 days	1.82	0.13	14.33	384	<0.001
	30 days–60 days	0.80	0.10	7.97	384	<0.001
Group 2	3 days–8 days	2.27	0.10	22.67	384	<0.001
	3 days–15 days	4.33	0.13	34.12	384	<0.001
	3 days–30 days	6.37	0.14	45.26	384	<0.001
	3 days–60 days	7.06	0.15	47.55	384	<0.001
	8 days–15 days	2.06	0.10	20.63	384	<0.001
	8 days–30 days	4.10	0.13	32.35	384	<0.001
	8 days–60 days	4.80	0.14	34.09	384	<0.001
	15 days–30 days	2.04	0.10	20.42	384	<0.001
	15 days–60 days	2.73	0.13	21.57	384	<0.001
	30 days–60 days	0.69	0.10	6.94	384	<0.001
3 days	Group 1–Group 2	−0.10	0.16	−0.64	384	>0.999
8 days	Group 1–Group 2	−1.69	0.16	−10.59	384	<0.001
15 days	Group 1–Group 2	−0.98	0.16	−6.12	384	<0.001
30 days	Group 1–Group 2	0.04	0.16	0.26	384	>0.999
60 days	Group 1–Group 2	−0.06	0.16	−0.38	384	>0.999

matrix and is present in high concentrations in cartilage and synovial fluid.[10]

Some authors claim that sodium hyaluronate, which is a defined fraction of hyaluronic acid, has analgesic and anti-inflammatory properties, contributes to the normalization of fluidity or viscoelasticity of the synovial fluid and to the activation of tissue regeneration in the affected cartilage, and restores the functional balance of the joint. Therefore, they recommend its use for the treatment of osteoarthritis.[4,13,14]

Some studies have reported that, in addition to relieving pain and improving function, the use of hyaluronic acid could alter the course of osteoarthrosis and improve qualitatively and quantitatively the articular cartilage. These indications are based on studies of imaging such as X-ray and MRI, in which there was an increase in cartilage volume and a decrease in joint space after the treatment *versus* placebo. These benefits are also based on the best quality of the matrix and on a higher density of chondrocytes in biopsy studies after the implementation of treatment.[4]

In animal studies, Plaas et al.[15] concluded that hyaluronic acid suppresses synovial hyperplasia and the development of periarticular fibrosis, and protect against cartilage erosion, and also acts to relieve pain in the short term (dilution of joint

Table 3 – Result of multiple comparisons of Lysholm questionnaire among groups and time points.

Group/time point	Comparison	Mean estimated difference	Standard error	t value	gL	p
Group 1	Pre–15 days	1.10	0.28	3.92	288	0.003
	Pre–30 days	−43.47	0.33	−133.55	288	<0.001
	Pre–60 days	−47.76	0.34	−140.79	288	<0.001
	15 days–30 days	−44.57	0.28	−158.49	288	<0.001
	15 days–60 days	−48.86	0.33	−150.11	288	<0.001
	30 days–60 days	−4.29	0.28	−15.24	288	<0.001
Group 2	Pre–15 days	12.02	0.28	42.74	288	<0.001
	Pre–30 days	−28.88	0.33	−88.72	288	<0.001
	Pre–60 days	−41.84	0.34	−123.34	288	<0.001
	15 days–30 days	−40.90	0.28	−145.43	288	<0.001
	15 days–60 days	−53.86	0.33	−165.47	288	<0.001
	30 days–60 days	−12.96	0.28	−46.08	288	<0.001
Pre	Group 1–Group 2	−1.73	0.35	−5.01	288	<0.001
15 days	Group 1–Group 2	9.18	0.35	26.54	288	<0.001
30 days	Group 1–Group 2	12.86	0.35	37.16	288	<0.001
60 days	Group 1–Group 2	4.18	0.35	12.09	288	<0.001

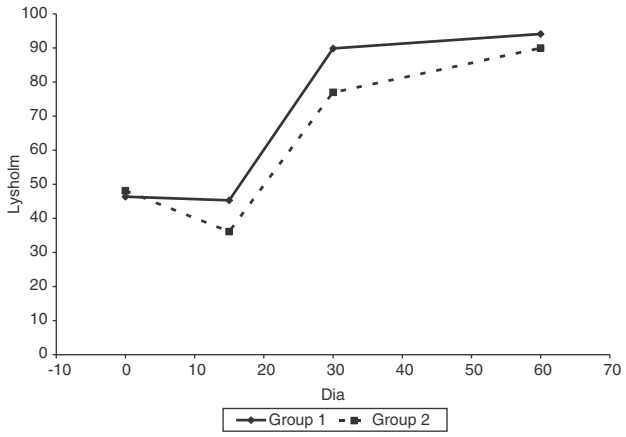

Fig. 2 – Graphical representation of the mean profiles and respective standard errors of Lysholm questionnaire, according to groups.

fluid) and in the long term (blocking of pain receptors), and improve the gait pattern of the osteoarthrosis knee.

Currently, the use of intra-articular hyaluronic acid is also widely discussed because of the different formulations, with different molecular weights and the results of some meta-analyses. These studies also differ in the parameter used and further increase the discussion as to the effectiveness of its use.[16]

Huang et al.,[13] in a randomized, double-blind, multicenter study, evaluated in one sample of the Asian population the use of intra-articular hyaluronic acid *versus* placebo. These authors found statistically significant improvement in reducing the pain and in the knee function, especially after the fifth week of treatment. These benefits have remained effective for up to 25 weeks. In the subjective evaluation, favorable results with its use also were noted. Regarding the consumption of acetaminophen and the volume of joint fluid, there was no statistically significant difference for any group.[11]

These results are consistent with the study by Navarro-Sarabia et al.,[17] in which there was a statistically significant difference in favor of hyaluronic acid in the categories of pain relief, improved function and overall improvement of the patient *versus* placebo.

Bannuru et al.,[14] in a meta-analysis comparative of the use of intra-articular hyaluronic acid *versus* placebo, concluded that hyaluronic acid is effective as early as the fourth week of treatment, with peak effectiveness at eight weeks, and remaining beneficial for up to 24 weeks. These authors evaluated the effectiveness for pain relief, improved function and decreased joint stiffness.

Lee et al.[18] believe that the analgesic effect of hyaluronic acid in the first five weeks is equal to that of placebo. In their prospective and randomized study, the authors concluded that the use of cetorolac associated with hyaluronic acid showed more rapid analgesia *versus* monotherapy with hyaluronic acid. In the fifth week this analgesia achieved equal intensity in both groups (hyaluronic acid with cetorolac × hyaluronic acid alone).

But it is worth bearing in mind that the aforementioned studies evaluate the hyaluronic acid in the treatment of osteoarthrosis; hence, it is interesting to quote them, because they discuss the efficacy of hyaluronic acid as a means of improving function and pain.

Regarding the use of hyaluronic acid in the post-operative of arthroscopy, Forster and Straw[19] compared pain and function in activities of daily living in patients with isolated arthroscopy *versus* arthroscopy associated with hyaluronic acid. These authors concluded that there was improvement of function with the use of HA, but without difference in the category of pain.

Heybeli et al.[1] compared pain and function in patients with 40–65 years old with mild to moderate osteoarthrosis and who underwent arthroscopy with and without the use of hyaluronic acid (HA) post-operatively. There was no statistically significant difference with respect to pain, but there was improvement in function in patients who used HA. In our study, we observed the same result with respect to function improvement, mainly until the 30th day, both by the Lysholm questionnaire and by the goniometer mensuration. However, with regard to pain, until the third day the results confirm the literature, with no difference with the use of the medication in question; thereafter, patients treated with hyaluronic acid had less pain *versus* control group, and this analgesia achieved equal intensity in the 30th day-evaluation and from then on.

Hempfling[10] also contrasted isolated arthroscopy *versus* arthroscopy associated with HA in the items of night pain, pain when walking, and ability to walk 100 meters without pain. A clear symptomatic improvement occurred in both groups, compared with preoperative values; but in the group using HA this improvement lasted longer. In our study, there was also significant improvement in pain and function *versus* preoperative assessments, but this difference was observed in the initial evaluations. After the 60th day, an important difference between the ratings of Groups 1 and 2 was not observed, which can be justified by the lack of assessment of patients over a longer period, when maybe we could observe results equivalent to the literature.

In 2007, Ulucay et al.[20] compared the use of three types of HA in women 40–60 years old with mild osteoarthrosis and degenerative meniscal lesion, after arthroscopy. These authors concluded that HA is effective therapy for these patients.

Also in 2008, Atay et al.[21] compared the effect of HA of high and low molecular weight *versus* placebo in terms of pain, stiffness and functional ability at six and 12 months after arthroscopic debridement in patients with mild to moderate osteoarthrosis. After six months, there was no statistically significant difference, but this occurred after 12 months. The authors concluded that the use of HA results beneficial and improves the effectiveness of treatment, regardless of the substance's high or low molecular weight. In our study, pain improvement was observed until the 15th day, with better range of motion and functional capacity until the 30th day. There was no statistical difference for the items evaluated from the 60th day.

Waddell and Bert,[2] in a systematic review conducted in 2010, concluded that more studies are necessary to support the use of HA in the post-operatory of knee arthroscopy patients. However, it seems that the use of HA helps to

decrease pain and improve the function of a significant number of patients post-operatively. In our study, the improvement of pain, function, and range of motion in patients who were treated with HA infiltration was observed. The improvement of pain is observed in the initial stage, especially until the 15th day; on the other hand, the function and range of motion improved after this period. We believe in a direct relation with this effect: with less pain, the patient can achieve a faster rehabilitation, with more quality, besides a faster return to his/her daily functions.

When interpreting more deeply the Lysholm questionnaire, our results demonstrated, in the initial evaluation, that although both groups were classified as poor, the superiority of the patients in Group 1 was justified by the best assessments in relation to pain and swelling. This finding corroborates the results of VAS and can be explained by the analgesic and anti-inflammatory effect of hyaluronic acid. [4,13,14]

In the 30th day evaluation, we found the greatest difference between Groups 1 and 2: 90 and 77 points, respectively. The main differences are in the item "swelling", again because the anti-inflammatory effect of HA. As of "claudication", "instability" and "squatting", we believe that, by this time, with a more effective therapy and because of a lower intensity of pain, it is possible that the patient be submitted to more intense demands and achieve an earlier gain of muscle mass and proprioception. This would facilitate the activities above evaluated. From the 30th, the pain was similar in both groups, and in the assessment of the 60th day both groups were classified as good, with statistical superiority in Group 1 *versus* Group 2 (94×90, respectively). This superiority was due to the improved ability to climb stairs by Group HA patients, likely due to the better muscle reserves acquired in the initial 60 days.

Conclusion

Given the subjective parameters evaluated, we believe that the use of intra-articular infiltrations of sodium hyaluronate 20 mg in procedures of arthroscopic surgery of the knee is fully justified, as this practice leads to a decrease in pain in the initial phase, enables faster patient recovery and generates a faster return and better quality to the activities of daily living.

Our study has some limitations: the short period of evaluation of patients (we were unable to verify the effects of hyaluronic acid in the medium and long term), and also the fact of the subjectivity of the evaluation of patients' function. This implies that perhaps an isokinetic evaluation with cybex could better demonstrate a muscle differences between the two groups of individuals. We believe that this is the main cause of improvement of the function on the 60th day. Unfortunately, we could not proceed with this option for lack of money.

Conflicts of interest

The authors declare no conflicts of interest.

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