The evaluation of Hilan GF-20 in the postoperative knee arthroscopies for arthrosis

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SUMMARY

This study evaluated the benefits of the Hylano GF-20 use in the postoperative period of knee arthroscopies for irrigation and debridement due to arthrosis. Twenty knees of twenty patients underwent arthroscopy. They presented arthrosis up to 3rd classification degree, pain and had their knees blocked. The segmental treatment showed no improvement ,consequently irrigation associated with mild condral and meniscus debridement was performed according to each case.

The patients were divided into two groups: arhtroscopy was performed in one; in the other, arthroscopy associated with the use of three weekly infiltrations of Hylano GF-20. The patients were evaluated according to the following variables: pain during night sleep; pain during movements with loads of 10% of the body weight; pain during more severe movements of the injured knee with visual scale and the daily amount of potassium diclofenac ingested to relieve the pain of the injured knee.The statistical results showed a significant improvement in relation to all studied variables of patients from the group submitted to the use of Hylano GF-20 infiltration in the postoperative period of knee arthroscopy due to arthrosis.

Keywords: *Knee; Arthrosis; Arthroscopy.*

INTRODUCTION

Osteoarthrosis is the most prevailing degenerative joint disease, resulting in significant morbidity and one of the highest treatment costs for the health systems worldwide[1,7,12,13]. The process of the disease is characterized by progressive erosion of joint cartilage, resulting in a decrease of joint space, subchondral sclerosis, formation of marginal osteophytes, subchondral cysts, and synovial inflammation resulting in pain and decreased function, leading these patients to search for medical care[1, 2,12].

The normal cartilage is an avascular tissue formed by a great extracellular matrix and sparse cells. Water amounts to 66 to 80% of its structure and the organic material consists of 48 to 62% of type-II collagen and 22 to 38% of proteoglycans. These groups of liquids of variable density, fibers with several directions, and cells distributed within are nurtured by soak, and its anabolic and catabolic process is governed by several factors, especially the growth factor. The homogeneity and the balance of that complex structure are maintained by several enzymes, in their majority secreted by chondrocytes and synovial cells. Arthrosis leads to balance disturbance and cartilage disorder due to its fragmentation, thus resulting in the release of degrading enzymes from the matrix by chondrocytes and, therefore, in the fibrillation and fragmentation and subsequently lesions of joint surface, such as cambers (arching) and ulceration of the cartilage[2, 9].

Knee arthrosis can be classified as primary (idiopathic) or secondary to inflammatory, infectious, or traumatic diseases that destroy the structure of the cartilage[2,9]. The initial classic treatment of the knee osteoarthrosis is conservative in general with the use of analgesic and antiinflammatory drugs, intraarticular injections of corticosteroids associated to physiotherapy and weight loss. However, with better, although partial, knowledge of ethiopathogeny, new drugs have been studied and recently used with relative success, aiming at the protection of the cartilage structure, as is the case with diacirein, glucosamine sulfate and chondroitin, and the unsaponifiable oils that seem to reduce the action of the degrading enzymes and protect the joint cartilage.

Loss of the elastoviscosity properties of the sinovial liquid plays an important role in the pathophysiology of osteoarthrosis. Therefore, hyaluronates have been developed for intraarticular infiltration and shown to be effective as a conservative treatment for arthrosis[2,7,9,12,13].

When conservative therapy fails, several surgical therapies are available, such as arthroscopy for lavage and joint debridement , corrective osteotomies, and partial or total arthroplasty of the knee, depending on the degree of the arthrosis[1, 2, 12]. The most controversial treatment mentioned in literature is lavage associated to joint debridement. Irrigation of the knee joint reduces the concentration of the lytic enzymes, removes debris from joint cartilage and free bodies, a theoretical source of persistent synovitis, which includes the adequate performance of meniscectomies leading to blockage and pain. Historically, debridements were first described by Pridie[10] and Magnunson[8] and were analyzed later by Insall[10]. Pridie[10] found 64% of success and Magnunson[10] described a fibrocartilaginous response following light debridement of the cartilage lesions. In addition, satisfactory results were found by Rand[10] (74%), Sprague[10] (75%), Bert and Macshka[10] (77%) and associated with the almost 500 cases of Insall[10]; folowing a retrospective review, conclusion was that lavage and debridement would be suitable in patients with symptoms of mechanical blockage. Hylan GF-20 (hyaluronate of high molecular weight) has been routinely used by orthopedic

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surgeons and given by intraarticular infiltration following arthroscopy for knee arthrosis. This procedure is carried out based on the fact that the sinovial liquid, in arthrosis of the knee, presents decreased viscosity and elasticity properties, as well as on the efficacy demonstrated by previous studies for the use of this drug in the conservative treatment of arthrosis[2,7,9,12,13].

The objective of this research was to evaluate benefits, if any, in the use of this drug for lavage and debridement in the postoperative arthroscopies.

CASUISTICS AND METHOD

Twenty patients presenting knee arthrosis refractory to conservative treatment with blockage and pain symptoms were studied. They were from the Clinic of Orthopedics from the Irmandade da Santa Casa de Misericordia de Sao Jose do Rio Preto, in the State of Sao Paulo, and they were submitted to arthroscopic treatment for articular lavage and debridement to articulate.

The study was performed from September 2002 to March 2003 and randomized patients into 2 groups.

In group I (10 patients), the behavior of treatment with arthroscopy (articular lavage and debridement) associated to the weekly postoperative infiltration, totaling three infiltrations, of Hylan GF-20 was studied. Nine patients were female and 1 male, with age range from 44 to 57 years (mean age: 52.80 years). Out of this total, seven presented an injury on the right side and three on the left side, and all the patients had arthrosis grade 3 of Kellgren and Lawrence[5] upon radiography examination.

In group II (10 patients), the behavior of treatment with arthroscopy (articular lavage and debridement) without the postoperative use of any condral protecting medication was studied in seven female patients and 3 male patients aged from 39 to 73 years (mean age: 56.10 years). Out of the total of 10 treated knees, six had an injury on the right side and four on the left side, and all the patients had arthrosis grade 3 Kellgren and Lawrence[7] upon radiographic examination. Computerized tomography showed chondral and meniscus injuries in all patients.

Patients from both groups were submitted to a previous evaluation of the knee to be operated. Clinical history, physical and radiographic data were assessed. The grade of pain reported during the rest at night, pain during movement with a 10% overload of the corporal weight and reduction of the pain during the most painful movements of the knee with visual analogical scale. In addition to these parameters, the number of potassium diclophenac tablets ingested daily for pain relief in the affected knee was also studied.

The Informed Consent form was supplied and explained by the Committee of Ethics in Research from FAMERP (Protocol no. 4119/2002) at the pre-treatment examination.

Only the patients classified as grade 3 Kellgren and Lawrence[5] were studied, due to the previous observation in the literature that the drug doesn't bring proven benefits to patients classified as grade 4 or 5[1,18]. Please find below the description of the Kellgren and Lawrence[5] classification of in its 5 degrees:

Grade 0 – No radiological alteration characteristic of osteoarthrosis.

Grade 1 - Presence of a minimum osteophyte without reduction of the articular space.

Grade 2 - Presence of a minimum osteophyte with low reduction of the articular space.

Grade 3 - Presence of moderate osteophyte with moderate reduction of the articular space.

Grade 4 – Articular space almost or totally reduced with sclerosis of the subchondral bone.

Patients with grade 3 upon Kellgren and Lawrence[5] radiological classification with blockage symptoms that did not improve with previous conservative treatment were then submitted to arthroscopic surgery for the necessary chondral lavage, debridement, and the partial or total meniscus stabilization. The technique used was the three portals (superomedial, inferomedial and inferolateral). Saline solution was used and the meniscus cartilage stabilization was softly made without abrasion, exposure or perforation of the subchondral bone. Patients were stimulated to stroll in the first postoperative day and stitches were removed at the first visit after two weeks. Patients from group I were submitted to 3 weekly infiltrations of Hylan GF-20 starting from the first follow-up consultation on; it was carried out with an anesthetic button (2 ml of Xylocaine at 2% without vasoconstrictor) on the skin, with a rigorous asepsis in the superolateral area of the operated knee. Patients from group II were not submitted to infiltration with Hylan GF-20. All patients were assessed at 2,4,8,16, and 24 weeks following surgery with the use of a visual analogical pain scale (ruler) where the side shown to the patient presented pain "faces" and colors ranging from blue to red as pain increased, and the observer's side showed the value assigned by the patient in absolute numbers (pain during the night rest, pain during movement with a 10% overload of weight on the affected knee and pain reduction during the most painful movements of the knee). The degenerative chondral lesions were classified at the moment of arthroscopy by Noyes and Stabler *appud* Lemark[6] as grade I: chondromalacia-type lesion, grade II: cartilage lesion without subchondral bone view, and grade III: osseous exposition. Statistical analysis was made at the Laboratory for Study Design and Data Analyses of the Department of Epidemiology and Public Health of the Medical School of Sao Jose do Rio Preto. Normal distribution of data was found, as shown by the graphs below. This was checked by the Anderson-Darling test, according Figure 1:

In order to compare 2 averages, the Welch t-test was used. The variance analysis for repetitive measurements was used for the comparison of the group and the effect, and group interaction x time. The use of this test was only possible due to the normal distribution followed by the groups. Significance level $\alpha = 0.05$, was adopted as usually seen in health sciences studies.

Patients	Age	Sex	Occupation	L	Drp	G	Cartilage
1	51	F	Servant	D	L3	I	CFM2
2	68	F	Housewife	D	L3	II	CFM2TL2
3	55	M	Driver	D	L3	I	CFM3TM3
4	45	F	Housewife	D	L3	II	CFL2TL3
5	53	F	Housekeeper	E	L3	I	CFM1TM1
6	60	F	Housewife	D	L3	II	CFM3TM3
7	44	F	Dressmaker	E	L3	I	CFM2
8	51	F	Housewife	E	L3	II	CFM3
9	51	F	Salesperson	D	L3	I	CFM2
10	73	F	Housewife	D	L3	II	CFM1
11	57	F	Servant	D	L3	I	CFM2
12	63	M	Militar	E	L3	II	CFM2
13	52	F	Housewife	D	L3	I	CFM2
14	39	F	Salesperson	E	L3	II	CFM2
15	57	F	Servant	D	L3	I	CFM2
16	45	M	Bricklayer	D	L3	II	CFM2
17	53	F	Housewife	E	L3	I	CFM2
18	47	F	Driver	D	L3	II	CFM1
19	55	F	Teacher	D	L3	I	CFM2
20	70	M	Street-swepper	E	L3	II	CFM2

Drp = radiologic diagnosis of the disease [Kellgren-Lawrence3
GG Classified group; cartilage (L) chondral injury; (F) femoral; (T) tibial; (M) medial; (L) lateral; (1,2,3) grade of the injury of Noves and Stabler

Table 1 - *Data of the 20 patients who were operated*

RESULTS

A larger number of female patients were found both in group I (9) and group II (7), with a p value of 0.58. Therefore, *there was no evidence of proportion difference* for women among the study groups.

Mean age was 52.80 years for group I and 56.10 for group II. Therefore, *there was no evidence* of average age difference among the study groups (p value=0.43).

By evaluating the results found for all variables in the preoperative assessment, it was observed that th*ere was no evidence* of mean difference during *the preoperative period*, as shown by Table 1:

By evaluating the results for all study variables at the first evaluation, no evidence of mean difference was found at the first *evaluation*, as show by Table 2:

By evaluating the results for all study variables at the first evaluation, it was observed that no evidences of mean reduction differences were found from the preoperative evaluation up to the first postoperative evaluation, as shown by Table 3:

By evaluating the results for all study variables from the first to the fifth evaluation, it was observed that *there was evidence of* reduction in the group I and of stability in the variables: pain in rest, pain with load and pain to the most painful movement, and an increase in the variable diclofenac in the group II from the first *to the fifth postoperative evaluation*, as shown by Table 4:

The degree of cartilage lesion found on the arthroscopies compared to the averages was assessed; it was noted that this should not be a limiting factor for the improvement found in group I (Figures 2 – 5)):

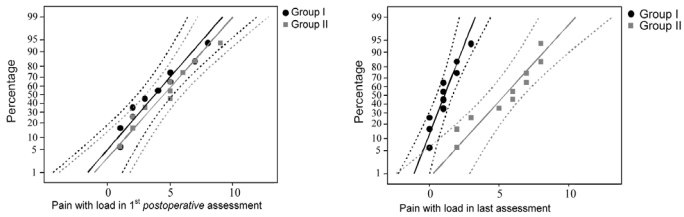

Figure 1- *Graphs of pain evaluation upon movement with 10% overload on corporal weight at the first and the last postoperative evaluation (Anderson-Darling method), showing a normal pattern. Welch t-test was used for comparison of 2 means.*

DISCUSSION

Articular cartilage lesions are the greatest challenges of Orthopedics today. As for knee arthrosis, the best treatment following conservative therapy failure has not yet been established, especially in mild to moderate arthrosis where osteotomy or arthroplasty would be indicated. The great problem with these treatments, in addition to the costs, are the serious risks involved, from clinical risks to those associated with implants, resulting in complications for the patients. Great divergence exists in literature, but the arthroscopy associated to the lavage and light debridement has still been used with great frequency and with good results all over the world[10].

The upcoming of chondroprotection drugs (diacirein, glucosamine sulfate and chondroitin, unsaponifiable oils and hyaluronates) bring new improvement possibilities in the final result of the arthroscopic treatment. Inhibition of interleukin-1 production, thus preventing that metalloproteases destroy the cartilaginous matrix would avoid, for some time, the need for correction of instabilities or deviations from the mechanical axles and would result in less aggressive treatments, with substantially reduced surgical risks.

As already known, an important element in the pathophysiology of osteoarthrosis is the loss of the elastoviscosity properties of the sinovial liquid due to decreased concentration and molecular size of hyaluronic acid. This considerably increases the susceptibility of cartilage to lesions due to overload; the use of hyaluronates in the postoperative arthroscopy for lavage and light debridement has become a possibility of improved results, due to the capacity of hyaluronates to reduce the pressure vector caused by the weight; to protect the integrity of the articular cartilage; to stabilize the cartilaginous matrix for the inhibition of proteoglycans loss and, as such, to intervene in the evolution of the tissue destruction process, improving the postoperative result of the referred chirurgical treatment[1, 2,9,12].

A certain tendency was observed in the world literature towards the use of Hylan GF-20, due to its largest molecular weight, because it would have an absorption power for larger weights than the one with low molecular weight, with better results in relation to the improvement of the pain and functional capacity of the knee[1,9,12,13]. Besides this physical property, it is believed that Hylan GF-20 also presents other theoretical properties that would aid in the improvement of the pain and of the functional capacity of the knee with arthrosis as described by Watterson and Esdaile[12] in their article:

- **Antiinflammatory property:** The hyaluronic acid is involved in the transduction of the surface receptors' signals of the leukocyte cells and that are dependent of the size of the hyaluronic acid molecule and, then, the administration of the same in the intra-articulation form would reduce the levels of the inflammatory mediators.

- **Analgesic activity:** Studies in experimental models using mice and cats, showed a reduction of the nociceptive activity in inflamed articulations, maybe due to the direct action in the synovia or indirectly through the substance P.

The idea of studying the behavior of the use of Hylan GF-20 in the postoperative knee arthroscopies for lavage and debridement was due to the continuous use by knee surgeons in an empiric way, and without scientific corroboration. In the attempt of finding support in the literature, only two studies to support that the use of hyaluronates of low or high molecular weight could be important in the postoperative knee arthroscopies, improving the postoperative results for these, were found.

Vad et al[11] tested the lavage of the knee with saline solution (performed at the clinic) previously to the infiltration of Hylan GF-

	Pain in rest	Pain with load	Pain upon the movement	Amount of diclofenac
Group I	7.90 (1.29)	8.60 (1.26)	8.40 (1.51)	2.80 (0.78)
Group II	8.30 (1.06)	9.20 (1.03)	9.10 (0.87)	2.50 (0.70)
Value-p	0.46	0.26	0.22	0.38

Table 1- *Mean values, standard deviation (sd) and p-value for all study variables in the preoperative assessment:*

	Pain in rest	Pain with load	Pain upon the movement	Amount of diclofenac
Group I	3.20 (1.75)	3.80 (2.44)	3.90 (2.13)	0.90 (1.10)
Group II	4.00 (2.49)	4.50 (2.51)	5.20 (2.25)	0.80 (1.03)
Value-p	0.42	0.54	0.20	0.84

Table 2 - *Mean values, standard deviation (sd) and p-value of all study variables at the first postoperative assessment.*

	Pain in rest	Pain with load	Pain to the movement	Amount of diclofenac
Group I	4.70 (1.89)	4.80 (2.39)	–4.50 (2.32)	–1.90 (1.29)
Group II	4.30 (2.58)	4.70 (2.75)	–3.90 (2.47)	–1.70 (1.34)
Value-p	0.7000	0.9300	0.5800	0.7400

Table 3 - *Mean values, standard deviation (sd) and p-value for all study variables from the preoperative evaluation up to the first postoperative evaluation.*

	Pain in rest	Pain with load	Pain to the movement	Amount of diclofenac
Group I	2.40	2.70	3.20	0.80
Group II	–0.70	–0.90	–0.10	–1.10
Value-p	0.019	0.0059	0.0021	0.001

Table 4 - *Mean values and p-value for all the variables from the first to the fifth postoperative evaluation.*

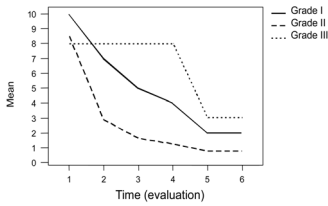

Figure 2 - *Pain during movement of 10% of body weight in group I for different grades of cartilage injury shown by arthroscopy*

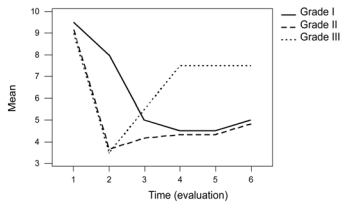

Figure 3 - *Pain during movement of 10% of body weight in group II for different grades of cartilage injury shown by arthroscopy*

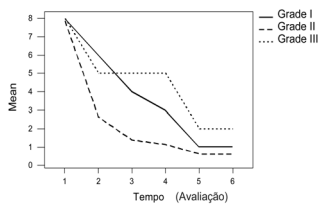

Figure 4 - *Pain at rest at night in group I for different grades of cartilage injury shown by arthroscopy*

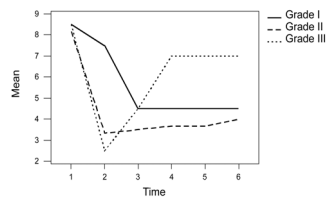

Figure 5 - *Pain at rest at night in group II for different grades of cartilage injury shown by arthroscopy*

20, with a control group just with Hylan GF-20 infiltrations separately for patients with knee arthrosis, and better results were observed in relation to the pain and functional capacity for the patients submitted to the previous lavage, in relation to the group in which Hylan GF-20 was used alone.

Daí et al[3] performed several weekly infiltrations of sodium hyaluronate in the postoperative surgical knee arthroscopies and found that the use of hyaluronate in the postoperative knee surgery seemed effective in the relief of the postoperative pain caused by the referred to surgeries.

In relation to the results found in our study, it was observed that there was no difference among the two groups in relation to sex and in relation to age average, which was in agreement with the world literature[2,9].

The statistical results found in the preoperative period evaluation showed that the groups didn't have a statistical difference in relation to the four studied variables, what demonstrated the homogeneity of the two groups studied.

In relation to the arthroscopic treatment, there were no intra or postoperative complications in the patients studied.

In relation to postinfiltration synovitis, the most common complication found in the literature with the use of Hylan GF-20, varying from 11% found by Puttick et al[8] and up to 47% by Henderson et al[4], this complication was not observed in the study performed.

In relation to the individual analysis of the first postoperative evaluation, a decrease of all the variables studied was observed in both groups, demonstrating that the surgical treatment was probably the differential factor in the improvement of the studied variables. Therefore, until that moment the infiltrations with Hylan GF-20 had not been made. This analysis is similar to the literature, and reports that there is improvement with the lavage and light debridement through arthroscopy.

In the statistical analysis, where the variables behaviors after or during the use of Hylan GF-20 were studied, an overall improvement or averages decrease trend was seen in group I compared to group II.

Data found here suggest that the degree of cartilage lesion (I - III by Noyes and Stabler) would not be a limiting factor for the improvement noticed, since an improvement or a decrease trend has always been observed in group I compared to group II.

Taking the statistical data into account, it was noticed that Hylan GF-20 was the differential of the improvement on study variables for both groups, and its routine use at the arthroscopy postoperative period for arthrosis treatment can improve its final outcome within the period of 6 months.

CONCLUSION

Taking into account the statistical data, Hylan GF-20 was responsible for the improvement seen in the study variables for both groups. The routine use following arthroscopy in the treatment of arthrosis can also lead to an improved outcome.

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