Intra-Articular Hyaluronic Acid in the Treatment of Osteoarthritis of the Knee: A Long Term Study

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Summary

A new therapeutic approach to the treatment of osteoarthritis is presented in this paper. We carried out a long term (30 months), open design study to assess the efficacy and tolerability of repeated courses of treatment with hyaluronic acid (HA) in patients with osteoarthritis of the knee. A total of 75 patients (35 males, 40 females) were included in the study. Treatment was one weekly, intra-articular administration of 20 mg/2 ml HA (Hyalart® - Fidia S.p.A., Abano Terme, Italy) for 5 consecutive weeks and this therapeutic schedule was repeated every 6 months over a period of 25 months. Hence, each patient received a total of 25 intra-articular injections. All 75 patients completed the study. Spontaneous pain decreased after the first treatment course and continued to decrease up to the end of the study when it showed an improvement of 55% compared with baseline values. The other pain parameters assessed also showed substantial decreases throughout the study. Joint flexion and extension showed a statistically significant improvement ($p < 0.05$) at the end of the study compared with baseline values. A substantial improvement was also observed for morning stiffness and supra-patellar circumference. The overall efficacy was judged as "very good" in 36 cases (48%), "good" in 30 cases (40%) and "poor" in 9 cases (12%). Neither local nor systemic adverse events were observed. Given the interesting results obtained, it would be appropriate to carry out controlled studies to confirm these promising findings.

Introduction

Osteoarthritis (OA) is the most common among the various articular disorders affecting man, and has many clinical causes. The nature of its initial morphological event is still unclear. However, in the intermediate and late stages of the disease, there is progressive destruction of articular cartilage leading to the exposure of sub-chondral bone at a weight-bearing site where the bone will then be subjected to abrasion and further damage.

The clinical results are pain, which is the most common and disabling problem experienced by patients with OA, joint effusion and a decrease in joint mobility. Pain management usually involves the use of analgesic and anti-inflammatory drugs. Analgesic drugs relieve pain and do nothing more[1]. In contrast nonsteroidal anti-inflammatory drugs (NSAIDs) not only reduce pain but also suppress inflammation and are preferred by physicians and patients for short periods of time. However, due to the well known side effects associated with the systemic use of these NSAIDs, they have to be used with great care especially in the elderly. In addition, NSAIDs have been shown to have a deleterious effect on cartilage metabolism[2,3,4]. Intra-articular injections of corticosteroids are also used in the treatment of osteoarthritis of the knee. There is some evidence that this may be of benefit particularly in patients where there is an acute inflammatory process associated with osteoarthritis and where more rapid relief of symptoms is required[5,6]. It is also valuable in treating soft tissue inflammation around the osteoarthritic joint, such as bursitis and tendinitis. Amelioration of pain may lead to overuse of the damaged joint aggravating cartilage breakdown. In addition, corticosteroids may also cause direct cartilage injury[7,8,9]. Thus repeated injections of corticosteroids into an osteoarthritic joint is probably not justified; injections should generally not be given more frequently than once every three months for a given joint[10].

The product Hyalart® (20 mg/2 ml HA), which has been developed for intra-articular administration in the symptomatic treatment of osteoarthritis of the knee and the hip, has recently become available in Argentina. Results of clinical studies conducted in Europe have demonstrated that the product combines short (1 month) and long term efficacy (2-6 months) with very good tolerability. However, these studies only used one treatment cycle. Given the beneficial symptomatic effects obtained with one treatment cycle in these studies, we felt it would be appropriate to evaluate the safety and efficacy of repeated treatment cycles in patients with osteoarthritis of the knee.

Materials and Methods

The aim of this open design study was to evaluate the long term (30 months) safety and efficacy of repeated treatment cycles of intra-articular injections of HA in patients with painful osteoarthritis of the knee.

Male and female patients with painful, clinically diagnosed osteoarthritis of the knee (ARA criteria), confirmed by X-ray assessments (Altman criteria), were included in the study. The clinical severity of the disease was assessed according to a three-point scale (1°=mild to 3°=severe).

Patients with the following characteristics were excluded from the study:

- Degenerative arthritis or other disease not related to arthritis (villonodular synovitis, Paget's disease, Sudeck's disease; neoplasm, recent trauma, etc.).

- Other severe diseases that might interfere with the efficacy of the test product.

- Ascertained or suspected pregnancy, lactation.

- History of allergies or hypersensitivity to drugs.

- Intra-articular injection, in the joint to be treated, during the 6 months prior to study entry.

- Diabetes.

Treatment was one weekly intra-articular injection of Hyalart® (20 mg hyaluronic acid sodium salt; excipients: 17.0 mg sodium chloride, 0.1 mg monobasic sodium phosphate $2H_2O$, 1.2 mg dibasic sodium phosphate $12H_2O$, water for injection q.s. to 2.0 ml) per week for 5 consecutive weeks. This therapeutic schedule was repeated every 6 months over a period of 2 years. Hence each patient received a total of 25 intra-articular injections of the test substance.

The following clinical parameters were used to assess treatment efficacy and were evaluated before each injection of Hyalart®, 90 days after the last injection of the treatment schedule, just before the start of a new therapeutic schedule, and at the end of the study: spontaneous day pain, using the Huskisson[15] 100 mm Visual Analogue Scale (VAS); pain at rest, night pain, pain on touch, pain on movement (all assessed using a 4-point scale: 0 = no pain, 1 = mild, 2 = moderate, 3 = severe; joint effusion (volume in ml aspirated by arthrocentesis to dryness); supra patellar circumference (cm); analgesic intake (paracetamol: 0 = never, 1 = occasionally, 2 = continuously); morning stiffness (in minutes); joint extension (in degrees using a goniometer), maximal flexion, maximal extension. In addition, X-ray assessments were carried out every 6 months. A global efficacy judgment was expressed by the patients and physician (poor, good, very good) at various times during the study and at the end of the study.

Drug safety was assessed by evaluating local or systemic side effects and by routine blood and urine analysis performed at the start of the study and every 6 months thereafter.

Statistics

Changes in the intensity of pain, morning stiffness and joint effusion were evaluated using the two-tail Student t-test and the Mann Whitney U test. The relationship between two conditions or states were analysed according to the z distribution. The relationship between the different categories were examined using the chi-square test. The mean values of more than two variables were compared using the analysis of variance (ANOVA) or the multiple analysis of variance (MANOVA) using Bonferroni's Method. The non-parametric values were analysed using the Friedman test and the assessment of any probable correlation between two variables was performed by the two minimum square method. The level of statistical significance was established at 5%.

Results

A total of 75 male and female patients (average age: 62.0 ± 9.0 for females and 55.2 ± 10.9 for males), who fulfilled the inclusion and exclusion criteria, were recruited into the study. All these patients presented radiologically confirmed osteoarthritis of the knee with pain symptoms. The disease stage was classified as: Stage 1: 9 patients; Stage 2: 46 patients; Stage 3: 15 patients and Stage 4: 5 patients according to the Altman criteria. The main characteristics of the patients are shown in Table 1. The mean duration of osteoarthritis was 5.8 ± 3.9 years. All the patients completed the study and no serious side effects were observed.

TABLE 1

Patient Characteristics at Baseline

	n	Age (years)	Weight (kg)	Duration of OA process (years)
		$x \pm SD$	$x \pm SD$	$x \pm SD$
Female	40	63.0 ± 8.1[1]	73.66 ± 11.1[2]	6.4 ± 4.2[3]
Male	35	53.1 ± 10.3[1]	81.90 ± 9.70[2]	4.9 ± 5.9[3]
Total	75	60.5 ± 10.1	75.49 ± 11.1	5.8 ± 3.9

Student t-test:
1 t= 3524; dof = 61; p<0.001
2 t= 2805; dof = 61; p<0.05
3 t= 2009; dof = 57; p<0.05

TABLE 2

Evolution of Spontaneous Pain During Treatment

		n	Mean VAS (mm)	s.d.
Female	Before treatment[1]		65	2.8
	After 1st treatment period[1]	40	39[2,3]	3.9
	End of trial[1]		29[2,3]	3.6
Male	Before treatment[1]		63	2.8
	After 1st treatment period[1]	35	42[2,3]	2.5
	End of trial[1]		28[2,3]	2.8

1 Friedman test: F: x^2 = 62281; dof = 2; p<0.001
 M: x^2 = 26233; dof = 2; p<0.05
2 Anova test F: p<0.001 M: p<0.001
3 Bonferroni test: F: p<0.05 M: p<0.05
M = Male F = Female

TABLE 3
Pain Symptoms

Parameters	Number of patients											
	Baseline (severity score)				After 1st treatment (severity score)				End of trial (severity score)			
	0	1	2	3	0	1	2	3	0	1	2	3
Night pain	-	13	42	20	2	39	30	4	22*	38	13*	2
Pain at rest	-	29	41	5	12	46	15	2	16*	46	14*	2
Pain on touch	-	30	42	3	8	46	18	3	14	49	11*	1
Pain on movement	-	10	50	15	4	19	50	2	6	21	46	2**

* = $p < 0.001$ (Friedman test)
** = $p < 0.05$ (Friedman test)

TABLE 4
Evolution of Joint Movement (in degrees)

		n	Mean Values (degrees)		s.d.
			Extension	Flexion	
Female	Before treatment[1]		163	72	26.8
	After 1st treatment period[1]	40	169	67[2,3]	26.6
	End of trial[1]		179	62[2,3]	26.4
Male	Before treatment[1]		165	69	26.6
	After 1st treatment period[1]	35	170	66[2,3]	29.4
	End of trial[1]		179	61[2,3]	25.3

1 Friedman test: F: $x^2 = 43870$; dof = 2; $p < 0.001$
   M: $x^2 = 18033$; dof = 2; $p < 0.05$
2 Anova test: F: $p < 0.001$ M: $p < 0.001$
3 Bonferroni test: F: $p < 0.05$ M: $p < 0.05$

TABLE 5
Suprapatellar Circumference (cm)

		n	Mean (cm)	s.d.
Female	Before treatment		42.5	3.1
	After 1st treatment period	40	41.6	2.6
	End of trial		41.0	2.3*
Male	Before treatment		42.9	3.9
	After 1st treatment period	35	42.6	2.7
	End of trial		42.0	2.6**

* = $p < 0.001$ ** = $p < 0.05$
(Bonferroni "t" test)

Primary efficacy parameter

The mean baseline values for the primary efficacy parameter, *spontaneous pain*, were 65 mm for the female patients and 63 mm for the males on the VAS (Table 2). This parameter showed significant improvements ($p < 0.001$), compared with baseline values, at 6 months after the first treatment cycle, and these continued throughout the study. The mean values for spontaneous pain at the end of the study showed an improvement of 55% compared with baseline values ($p < 0.001$).

Secondary efficacy parameters

The secondary efficacy parameters also showed a similar trend with a marked improvement 6 months after the first treatment cycle, this improvement continuing up to the end of the study. At baseline all patients presented pain of varying intensity for the parameters *night pain, pain at rest, on touch and on movement* (Table 3, Figure 1).
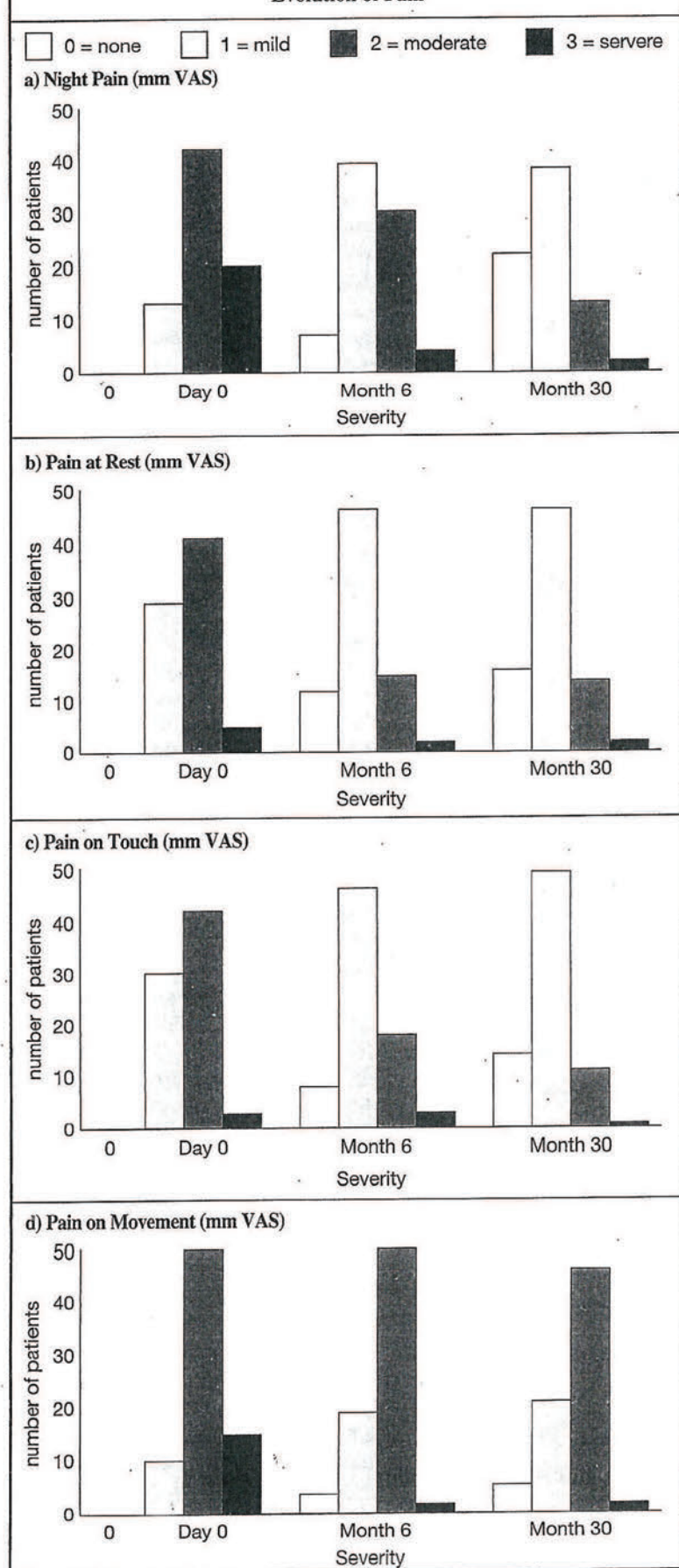
While most had mild to moderate pain, 20 patients reported severe night pain and 15 reported severe pain on movement. These symptoms improved greatly after the first treatment cycle and continued to improve throughout the study. Only 4 patients reported severe night pain and 2 patients reported severe pain on movement after the first treatment cycle. At the end of the study, 22 patients were free from night pain, 16 from pain at rest, 14 from pain on touch and 6 from pain on movement.

Joint flexion and *extension* improved after the first treatment cycle (Table 4) and throughout the study with a statistically significant difference ($p < 0.05$), compared with baseline values, at the end of the study.

At baseline, 35 patients presented *joint effusion*. This number decreased after the first treatment cycle and the improvement continued up to the end of the study when only 5 patients presented effusion ($p < 0.05$). It is interesting to note that these 5 patients presented stage IV OA at baseline and that the volume of effusion aspirated at the end of the study was much lower than the baseline values (Figure 2).

The supra-patellar circumference showed a significant decrease at the end of the study ($p < 0.001$ for females; $p < 0.05$ for males) (Table 5).

FIGURE 1
Evolution of Pain

☐ 0 = none   ☐ 1 = mild   ■ 2 = moderate   ■ 3 = servere

a) Night Pain (mm VAS)

b) Pain at Rest (mm VAS)

c) Pain on Touch (mm VAS)

d) Pain on Movement (mm VAS)

An improvement in *morning stiffness* was observed in about 80% of patients during the study period. This improvement was particularly evident after the third injection of the first therapeutic cycle and was maintained for the rest of the study.
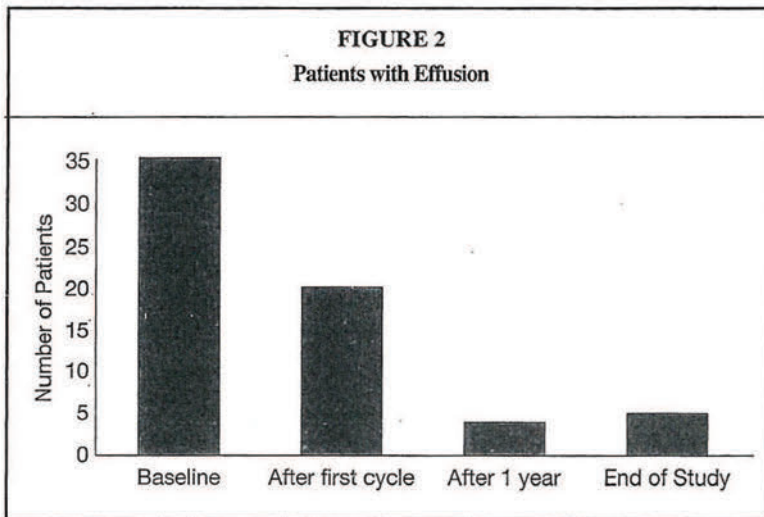
The intake of *escape medication* also decreased throughout the study. At baseline, 40% of patients took paracetamol (the only analgesic permitted) and this decreased to 5% at the end of the study.

Both the patients and the investigator expressed their judgement on the efficacy of the treatment at various times during the study. In general, these judgements showed a similar trend during the study and were favourable from Day 21 onwards, becoming progressively more favourable up to the end of the study. After the first treatment course of 5 injections, 60% of the patients were judged to have achieved good and very good improvement. By the end of the study 88% achieved good and very good improvement. The differences, compared with baseline values, were statistically significant (p = 0.05). However, there was no evidence of improvement in 12% of the cases.

No serious local or systemic effects were observed following repeated cycles of intra-articular injection of HA. Five patients complained of local pain after intra-articular injection. This effect lasted no longer than 72 hours and treatment was not interrupted in any of these cases.

Discussion

Hyaluronic acid (Hyalart®) has recently been introduced in Argentina for the treatment of osteoarthritis of the knee. Published clinical data show that HA caused significant improvements in pain symptoms and joint mobility. Although the onset of these improvements was not immediate as with symptomatic rapid acting drugs such as intra-articular corticosteroids, they were significant after the third intra-articular injection of HA and improved further during the study. Moreover, unlike corticosteroids, the beneficial effects of HA were long lasting (2-6 months in most studies) after treatment interruption indicating a long carry-over effect. Due to its mode of action, the International League for Associations against Rheumatism (ILAR) has classified intra-articularly administered HA as a symptomatic slow acting drug for osteoarthritis (SYSADOA)[11].

FIGURE 2
Patients with Effusion

[Bar chart: Number of Patients on y-axis (0–35), with bars for Baseline (~35), After first cycle (~20), After 1 year (~4), End of Study (~5)]

free from night pain, 12 from pain at rest, 8 from pain on touch and 4 from pain on movement. By the end of the study 22 patients were free from night pain, 16 from pain at rest, 14 from pain on touch and 6 from pain on movement. In patients still reporting pain, the severity of the pain symptoms had decreased. While 20 patients presented severe night pain at baseline, this was present in only 2 patients at the end of the study. These results are important as night pain also affects sleep and mood. Of the 15 patients that presented severe pain on movement at baseline, only 2 patients reported this symptom after the first treatment cycle and at the end of the study.

The long carry-over effect is not only due to improved joint lubrication or the mechanical effects of HA. Evidence now indicates that HA also has analgesic and anti-inflammatory properties[12]. In fact, intra-articularly administered HA has been shown to play an important role in reducing joint inflammation in patients with osteoarthritis of the knee (Corrado and Peluso, in this issue), causing the near normalisation of the viscous and elastic moduli of the synovial fluid after 5 intra-articular administrations[13], improving the barrier function of the synovium and reconstructing the protective HA layer around the cartilage[14]. These effects were seen after one treatment cycle of 5 intra-articular injections of HA.

We carried out a long term efficacy and tolerability study to evaluate the effects of cycles of HA treatment, repeated at 6-month intervals, over a period of 2 years in patients with osteoarthritis of the knee. Each patient therefore received 5 treatment cycles (a total of 25 intra-articular injections) with the final follow up visit being carried out at 30 months i.e. 5 months after the final injection.

Results showed that pain and joint movement improved significantly following treatment with HA with the beneficial effects lasting up to 6 months after the end of a treatment cycle. Significant improvements were already evident after the third injection of the first treatment course when pain, morning stiffness and joint effusion decreased significantly compared with baseline values, confirming the results of studies carried out in Europe.

However, an interesting finding was that repeated treatment cycles caused further symptomatic improvements, especially in patients with early stage OA, without accelerating joint damage.

An important aspect in OA patients is their psychological status as depression is often a feature of chronic pain. The results of our study show that treatment with HA significantly reduces pain in OA patients. At baseline, all patients reported night pain, pain at rest, pain on touch and pain on movement. Six months after the first treatment cycle, 7 patients were

Joint effusion decreased significantly during the study. While 35 patients presented joint effusion at baseline, this was present in only 5 patients at the end of the study. Joint mobility also improved significantly after the first treatment cycle and showed further improvements by the end of the study. No adverse reactions were observed throughout the study even though each patient received a total of 25 intra-articular injections of HA over a two-year period. In addition, no patient showed a deterioration in his or her condition.

The results of this study demonstrate that repeated intra-articular administration of HA (Hyalart®) is safe and effective and confirms that the product is a valid alternative in the treatment of patients with osteoarthritis of the knee.

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