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Intra-articular treatment of osteoarthritis of the knee: an arthroscopic and clinical comparison between sodium hyaluronate (500-730 kDa) and methylprednisolone acetate

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Abstract Corticosteroids have long represented the drugs of choice for intra-articular treatment of osteoarthritis (OA), but their use has drawbacks, indicating the need for alternatives devoid of these effects. This comparative study examined the clinical efficacy and the structural effects of intra-articular injections of sodium hyaluronate (HA) of molecular weight (MW) 500–730 kDa (one injection weekly for 5 weeks) versus methylprednisolone acetate (MP) (one injection weekly for 3 weeks) in the treatment knee OA. We studied 99 patients with knee OA, primary or secondary to a traumatic event, classified according to criteria of the American College of Rheumatology. Pain assessments by VAS and arthroscopic examinations of synovial membrane and cartilage were performed at baseline and 180 days after the start of the treatment. Arthroscopic features were evaluated under blind conditions. Initially, MP showed a more immediate beneficial clinical effect in reducing pain than HA, but after 180 days the symptomatic effect of HA was more long lasting than that of MP. Arthroscopic findings at day 180, in comparison with baseline conditions, showed that both drugs were decreased synovial membrane inflammation but HA was superior to MP in reducing the grade and extent of cartilage damage. HA of 500–730 kDa represents a valid alternative to corticosteroids in the intra-articular treatment of OA with a beneficial effect on the structural alterations. This study supports previous data on a potential structure-modifying activity of HA in OA of the knee.

Key words Arthroscopy • Hyaluronic acid • Intra-articular treatment • Methylprednisolone • Osteoarthritis • Structure modification

Introduction

Osteoarthritis (OA) is a degenerative joint disease common among elderly people, affecting particularly the knee and hip [1]. Its prevalence increases significantly with age: about 68% of women and 58% of men aged 65 years or older have radiological evidence of disease [2]. OA involves primarily the cartilage and the underlying bone, although synovial inflammation may be also present. Conventional treatments of OA are mainly aimed at reducing pain and ameliorating function, thereby improving the quality of life. To this end, intra-articular injections of steroids have been widely used, particularly in the past. Their use is controversial as their efficacy has not been always demonstrated and deleterious effects on cartilage have been reported experimentally even though never shown in humans [3, 4]. Therefore, the use of intra-articular steroids is currently restricted to the acute phase of OA, when local inflammation with severe joint effusions is present [5].
Intra-articular hyaluronic acid (HA) has been proposed as an alternative to steroids and non-steroidal anti-inflammatory

drugs (NSAIDs) for the intra-articular treatment of OA [5]. Experimental studies have provided evidence that HA of molecular weight (MW) of 500–730 kDa has several biological effects on joint tissues, including preservation of chondrocyte vitality and cartilage structure, and reduction of synovial cell proliferation in animal OA models [6–9]. Numerous clinical trials in patients with OA of the knee have shown that this HA can reduce pain and functional limitation [10–17], as well as slow down the progression of cartilage lesions as assessed by arthroscopic and radioscopic evaluations [18–20].

The present study compared the efficacy and tolerability of this HA (MW 500–730 kDa) versus intra-articular methylprednisolone on clinical outcome and on structural features in patients with primary or secondary knee OA.

Materials and methods

Patients

We considered for study outpatients who had been referred to the Rheumatology Unit (Department of Internal Medicine, Maggiore Hospital, Bologna, Italy), usually by the family doctor, for OA over a period of 3 years. The total number of patients recruited into the study was determined considering a 50% drop-out for a second arthroscopic procedure.

A total of 99 consecutive outpatients affected by primary OA (n=50) or OA secondary to traumatic events (n=49) to the knee, with Kellgren-Lawrence grades I-III [21] and fulfilling the clinical and radiological criteria of the American College of Rheumatology [22] were admitted to the trial. Patients judged not controllable or unreliable, those with presence of severe concomitant diseases, suspected joint infection, concomitant treatment with NSAIDs, intra-articular steroid treatment in the previous 3 months, pregnancy and breast feeding were excluded from the trial. The diagnosis of OA was confirmed by arthroscopy. When the OA was bilateral the most severely affected knee was selected for treatment.

The study was approved by the local ethics committee of Maggiore Hospital in Bologna and all patients gave written informed consent to participate in the study.

Study design and evaluation criteria

This was a 6-month, randomized, controlled study in which arthroscopic assessments were evaluated under blind conditions.

At admission, patients eligible for the study underwent an initial knee arthroscopy examination. In the following 2-4 weeks, patients were randomly assigned to one of two treatment groups according to a randomized scheme generated by computer. Patients received by intra-articular injection either 20 mg (in 2ml) of hyaluronic acid (HA, 500–730 kDa, Hyalgan, Fidia, Padua, Italy) once a week for 5 weeks or mg/ml methylprednisolone acetate (MP, Depo-Medrol, Pharmacia & Upjohn, Milan, Italy) once a week for 3 weeks.

Clinical symptoms and signs (nocturnal pain, pain at rest, pain on spontaneous or forced movement, pain on touch, morning stiffness, joint motion) were evaluated at baseline, during treatment at each visit before the injection of HA or MP, and in the follow-up (at days 0, 7, 14, 21, 28, 35, 60, 120, 180). At baseline and at day 180, blood and urine samples for routine laboratory assessment were collected. On day 180, if the patient agreed, a second arthroscopy examination was performed.

In order to maintain blind conditions, all arthroscopies were performed by the same investigator and videotaped. At the end of the study, a second investigator, neither involved in intra-articular injections nor in clinical evaluations, examined the videotapes. The arthroscopic assessment was performed under blind conditions by removing any information regarding patient, treatment received, and time of the arthroscopy. Each videotape was assigned a number generated from an appropriate randomization list.

Arthroscopic procedures

Arthroscopes (Hamou-Storz or Microview-Wolf), adapted from microhysteroscopes (4-mm diameter, 20-cm length) by modification of the lever arm, with a 90° field of vision, a 30° oblique lens and up to 150-fold magnification of the normal field were used. The resolution of these instruments (~1.5 μm) is comparable to that of a standard optical microscope at 150x. The depth of field used for observation of the synovial architecture and the terminal capillary pattern was ~80 μm. The light intensity used for direct observation, flash photographs and videorecording varied between 150 and 1000 W. Images were taken using an Olympus OM2 camera with appropriate Storz lens and an Ikegami ITC-370 M videocamera connected to a Sony U-Matic V 0-5800 PS videorecorder. Local anesthesia was obtained by intradermal injection of 2% mepivacaine HCl without a vasoconstrictor. The arthroscope was then introduced anterolaterally (subpatellar pathway) with the knee flexed at an angle of 30°. The joint cavity was intermittently irrigated with Ringer's acetate solution with an infusion pressure regulated to optimize its distension. The endoscopic examination started at a magnification of 1x to allow a wide-angle view similar to that offered by a conventional arthroscope. For microarthroscopic examination, 3 ml of a 1% aqueous solution of methylene blue (pH 4.5) was injected, followed after 5 min by a saline wash. The synovial membrane was examined in detail at 20x magnification, while its structure was examined at 60x magnification. Finally, a 150x magnification was used for the examination of the cellular components of the lining and subintimal layers.

Synovial membrane appareance was assessed using a method previously described [23] in which a total score ranging between 0 and 100 is obtained by adding three partial scores related to: (1) macroscopic characteristics, (2) vascularization and (3) cell density and shape.

A modified version of the Outerbridge and Noyes scales [24, 25] was used to evaluate the degree and the extent of cartilage damage in each compartment of the knee. Briefly, the *degree* of cartilage damage was assessed by using the following 5-point scale: grade 0, intact cartilage; grade I, apparently smooth surface, frosted glass aspect, softening, flaking; grade II, fibrillation, fissures, velvety aspect; grade III, tortuous ravines, fissuring; grade IV, extensive

and deep erosion with exposure of subchondral bone. The *extent* of cartilage lesions was assessed by using the following 6-point scale, related to the percent of the total compartmental surface involved: 0, no lesion; 1, up to 20% of surface involved; 2, 21%–40% of surface involved; 3, 41%–60% of surface involved; 4, 61%–80% of surface involved; 5, more than 80% of surface involved.

Clinical evaluation

The following clinical efficacy outcomes were considered: nocturnal pain, pain at rest, pain on spontaneous or forced movement, pain on touch (all measured on a visual-analog scale (VAS) ranging from 0 to 100 mm), morning stiffness, and maximum active extension and maximum active flexion measured in degrees using a goniometer from flat angle (180°). The use of an analgesic or NSAID, as well as the opinion of patients and physicians on efficacy [evaluated on a scale from 0, (poor) to 4, (excellent)] was recorded.

Safety criteria

The tolerability of treatment was assessed by monitoring adverse events (any signs and symptoms referred by the patients) and performing standard hematological and biochemical tests and urinalysis at baseline and at the end of the study (day 180).

Statistical analysis

Clinical data regarding pain (joint motion, morning stiffness) and arthroscopic parameters were assessed for differences versus baseline at various times by analysis of covariance (ANCOVA). Analgesics and NSAIDs consumption and clinical judgements were all evaluated by chi-squared test of Cochran Mantel-Haenszel. Values of $p<0.05$ were considered statistically significant.

Results

The demographic and disease characteristics of the 99 patients included in the study are reported, divided for treatment, in Table 1. The two groups were similar for both demographic and clinical characteristics of OA.

Of the 99 patients admitted, 16 (6 of HA group and 10 of MP group) withdrew from the study within the first 35 days and 13 (8 of HA group and 5 of MP group) during the follow-up phase for different reasons (5 did not complete treatment, 2 underwent surgery for concomitant illness, 1 withdrew because of adverse events, 11 refused to continue treatment and 10 were lost for unknown reasons). Seventy patients (38 of HA group and 32 of MP group) completed the 6-month study. Of these, 15 patients refused the second arthroscopy. Thus, a total of 55 patients (30 HA-treated and 25 MP-treated) who accepted to undergo both initial and final arthroscopic procedures have been evaluated in the arthroscopic data analysis. For clinical evaluations, all randomized patients were considered.

Table 1 Demographic and osteoarthritis (OA) characteristics of the 99 patients randomized to receive treatment with hyaluronic acid (HA) or methylprednisolone (MP)

	HA (n=52)	MP (n=47)
Men, n (%)	24 (46)	22 (47)
Age, years[a]	49 (15)	50 (14)
Weight, kg[a]	74 (10)	72 10)
Height, cm[a]	166 (7)	167 (6)
Diagnosis, n (%)		
Primary (OA)	23 (44)	27 (57)
Secondary (OA)	29 (56)	20 (43)
Severity, n (%)		
Mild	16 (31)	12 (26)
Moderate	34 (65)	29 (62)
Severe	2 (4)	6 (13)
Kellgren-Lawrence grade		
I	10 (19)	16 (34)
II	27 (52)	21 (45)
III	15 (29)	10 (21)
Duration of disease, months[a]	27 (23)	23 (25)

[a]Values are mean (SD)

Arthroscopic and microarthroscopic findings

At baseline, all 55 subjects showed clear inflammatory changes in the *synovial membrane*, which always appeared rough and edematous with opaque areas. The vascular network was markedly increased compared to normal. The vessels, either rectilinear or looping, were dilated and sometimes ectasic. There was marked cellularity, with prevalence of stellar and dendritic cells, but with the presence of numerous oval and round cells typical of inflammatory changes. At baseline there were no differences in the arthroscopic and microarthroscopic appearances of the synovial membranes between the two groups. The total score reflecting changes was 46.3 ± 6.0 in HA group and 46.4 ± 7.6 in MP group. At the final visit (day 180), the total score was reduced to 34.7 ± 6.0 in HA group and to 35.6 ± 6.5 in MP group, without statistically significant differences between groups.

At baseline, all 55 patients showed lesions of the *articular cartilage* in one or more knee compartments. At day 180 (Table 2), a statistically significant difference in favor of HA was achieved for the reduction in lesion extent in the

Table 2 Changes in arthroscopic scores for grade of cartilage damage and extent of cartilage lesion, from baseline to day 180 in 55 patients treated with hyaluronic acid (HA) or methylprednisolone (MP). Values are number (percentage) of patients

	HA (n=30)		MP (n = 25)	
Compartment	Grade	Extent	Grade	Extent
Medial femoral condyle				
Improved	13 (43)	9 (30)	4 (16)	4 (16)
Unchanged	17 (57)	21 (70)	20 (80)	21 (84)
Worsened	0 (0)	0 (0)	1 (4)	0 (0)
Medial tibial plateau				
Improved	8 (27)	8 (27)	3 (12)	1 (4)
Unchanged	22 (73)	22 (73)	22 (88)	24 (96)
Worsened	0 (0)	0 (0)	0 (0)	0 (0)
Lateral femoral condyle				
Improved	3 (10)	2 (7)	2 (8)	1 (4)
Unchanged	27 (90)	28 (93)	23 (92)	23 (92)
Worsened	0 (0)	0 (0)	0 (0)	1 (4)
Lateral tibial plateau				
Improved	3 (10)	3 (10)	3 (12)	2 (8)
Unchanged	27 (90)	27 (90)	22 (88)	23 (92)
Worsened	0 (0)	0 (0)	0 (0)	0 (0)
Patella				
Improved	17 (57)	11 (37)	5 (20)	5 (20)
Unchanged	13 (43)	19 (63)	18 (72)	20 (80)
Worsened	0 (0)	0 (0)	2 (8)	0 (0)
Trochlea				
Improved	6 (20)	3 (10)	4 (16)	4 (16)
Unchanged	24 (80)	27 (90)	21 (84)	21 (84)
Worsened	0 (0)	0 (0)	0 (0)	0 (0)

medial tibial plateau ($p<0.03$) and in lesion grade in the patellar compartment ($p<0.02$). For all the other compartments there was a tendency for a better improvement in the HA group than in the MP group. None of the patients in the HA group showed a worsening of cartilage lesions after treatment. By contrast, the grade and extent of cartilage lesion worsened in 3 and 1 patients of MP group, respectively (Table 2).

If we consider the subgroup with primary OA separately, significant differences in the changes from baseline to day 180 were found for extent of lesions in the medial tibial plateau and patella ($p<0.03$) and for grade in the patella ($p<0.01$).

Clinical efficacy

Nocturnal pain, pain at rest, pain on spontaneous or forced movement, and pain on touch were similar in the two groups at baseline and were progressively reduced by both treatments. In general there was an initial statistically significant difference ($p<0.05$) in favor of MP at day 35, but not at day 180. The effect of HA on pain appeared more gradually but lasted longer than that of MP (Fig. 1 reports pain scores after spontaneous and forced movements as examples of the patterns observed).

Maximal flexion movement was increased on average by 1.96 degrees in HA group and 3.90 degrees in MP group on day 35 and by 3.29 degrees in HA group and 4.38 degrees in MP group on day 180. Maximal extension movement was increased on average by 0.22 degrees in HA group and 1.49 degrees in MP group on day 35 and by 0.79 degrees in HA group and 1.43 degrees in MP group on day 180. There were no statistically significant differences between groups at day 180 in neither the parameters.

The duration of morning stiffness at baseline was 3.4 ± 6.7 min in HA group and 4.5 ± 8 min in MP group. On day 35 it was still present in some patients but absent in all patients on day 180.

One patient of each group used NSAIDs regularly throughout the study, while one patient of HA group on NSAIDs since baseline discontinued use by day 35. No other patient of either group took analgesic drugs during the entire study.

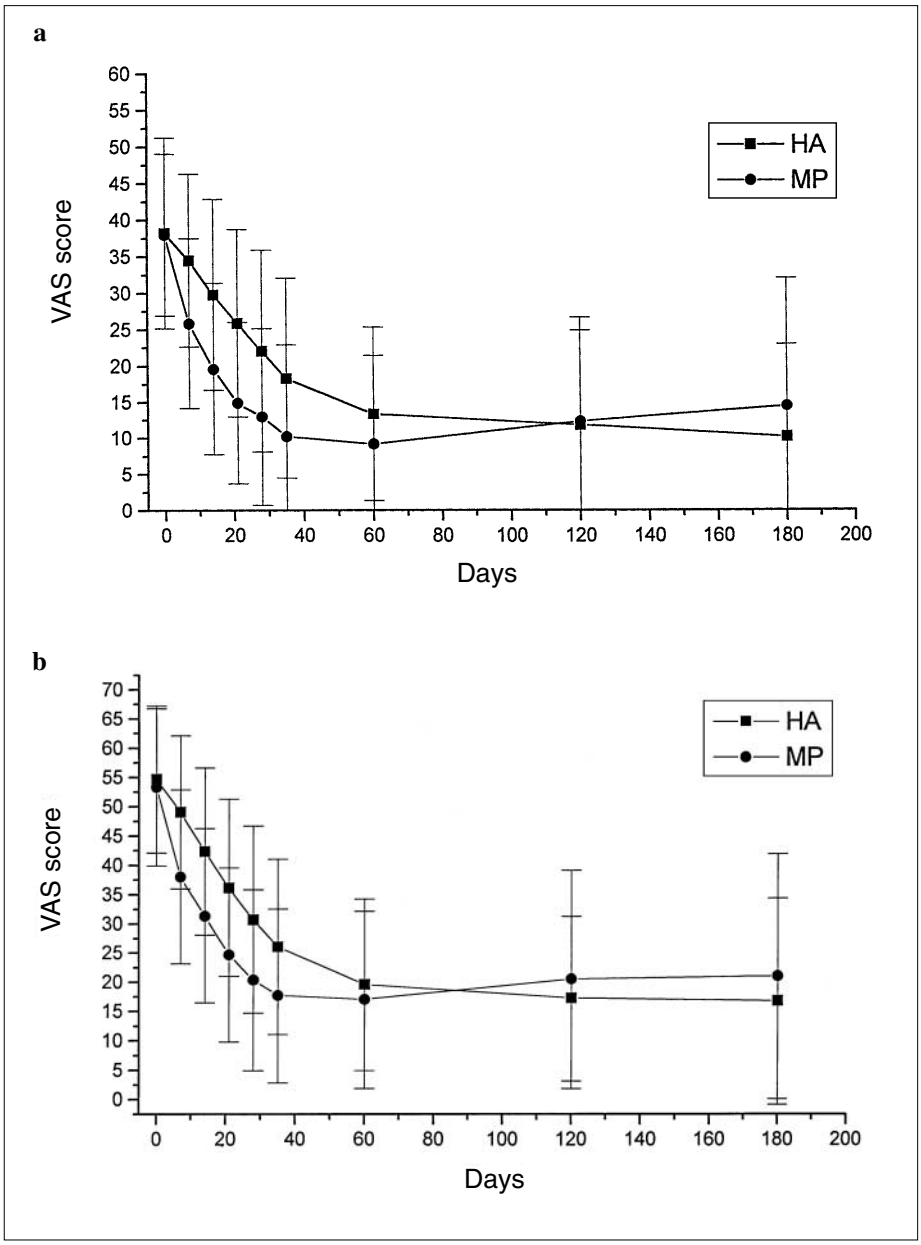

Fig. 1a, b The effects of intra-articular hyaluronic acid (HA) or methylprednisolone (MP) at various times on pain measured on a 100-mm visual analog scale (VAS) in 99 randomized patients. **a** Pain after spontaneous movement. **b** Pain after forced movement. Values are mean and SD

Physician and patient opinions reflected the course of clinical parameters, with a statistically significant difference in favor of MP on day 35 ($p<0.005$ and $p<0.001$, respectively) but not on day 180 (Table 3). This reflected the course of clinical parameters: a prompt but transient better efficacy of MP and a slower efficacy at the beginning but more persisting and prolonged in the time of HA.

Safety

One patient of the MP group withdrew from the study due to adverse reactions (malaise, tachycardia and hypotension) and one other of this group had gastric malaise. Both events occurred after the first MP injection. No adverse events were observed in the HA patients.

No clinically significant changes occurred in the laboratory parameters or other vital signs in either group.

Discussion

This study confirms and extends the results of previous clinical studies showing that HA of MW 500–730 kDa has beneficial effects similar to those of MP in reducing pain in patients with primary or secondary OA [15, 17]. The effect

Table 3 Physicians' and patients' evaluations at day 35 (one week after the last injection) and at day 180 (final visit) for all patients receiving hyaluronic acid (HA) or methylprednisolone (MP)

Score	Day 35		Day 180	
	HA (n=46)	MP (n=37)	HA (n=38)	MP (n=32)
Physicians' evaluations, n (%)				
0, unsatisfactory	1 (2)	1 (3)	1 (3)	4 (13)
1, scarce	7 (15)	1 (3)	3 (8)	3 (9)
2, fair	20 (43)	8 (22)	5 (13)	3 (9)
3, good	17 (37)	20 (54)	19(50)	14 (44)
4, excellent	1 (2)	7 (19)	10 (26)	8 (25)
Patients' evaluations, n (%)				
0, unsatisfactory	1 (2)	0 (0)	1 (3)	4 (13)
1, scarce	7 (15)	2 (5)	3 (8)	3 (9)
2, fair	17 (37)	3 (8)	4 (11)	1 (3)
3, good	19 (41)	24 (65)	18 (47)	14 (44)
4, excellent	2 (4)	8 (22)	12 (32)	10 (31)

of MP was prompt but short living. On the contrary, the effect of HA appeared more gradually but lasted longer than that of MP. Furthermore, arthroscopic and microarthroscopic examinations showed that HA is more effective than MP in reducing some of the inflammatory pictures of synovial membrane and in reducing the progression of cartilage lesions in OA.

Corticosteroids have long represented the drugs of choice for intra-articular treatment of OA, but their use has drawbacks [3, 4]. This observation indicates the need to find viable alternatives for intra-articular treatment which may be devoid of these effects. HA of MW 500–730 kDa can be regarded, for its biological characteristics, as a valid alternative to corticosteroids in the intra-articular treatment of OA. The therapeutic rationale of its use is described in the following paragraphs.

In the joint, HA, a natural linear polysaccharide, is a major component of the extracellular matrix of the cartilage. It is present in the superficial layers of the synovial membrane and it is found at high concentration in the synovial fluid [26, 27]. HA plays a key role in preserving the structural and functional integrity of the cartilage matrix and in regulating of a variety of cellular activities through specific cellular receptors and molecular interactions besides maintaining the viscoelastic properties of synovial fluid [27]. In vitro and in vivo studies have shown that HA of MW 500–730 kDa is able to induce proteoglycan synthesis and aggregation, stimulate synoviocytes to produce more HA, modulate the inflammatory response, reduce chemotaxis and leucocyte migration and exert scavenger activity on free oxygen radicals [26–31]. These activities are mediated by the binding of HA with intercellular adhesion molecule (ICAM)-1, CD44 integrin and the receptor for hyaluronic acid-mediated motility (RHAMM), all of which are expressed on the surface of varoius cell types, including inflammatory cells, synoviocytes and chondrocytes [26].

HA injected in the joint has a half-life of approximately 20 h when joints are normal and about 12 h when joints are inflammed [26]. Therefore, it can be excluded that the sustained beneficial effects of HA on symptoms and clinical signs of OA can be accounted only for a temporary restoration of the synovial fluid viscoelasticity. All the above evidence demonstrates that the clinical effects of this HA are due to its pharmacological action on the cellular and tissue components of the joint. Moreover the effects are MW-dependent since HA in the range of 500–730 kDa was more effective than HA of higher MW (>2300 kDa) in restoring synovial fluid rheological properties and synovial fibroblast metabolism and in reducing cartilage and bone pathology in animal OA joints [9].

Controlled clinical studies vs. placebo and intra-articular steroids have shown that HA of MW 300–730 kDa is effective in OA treatment as it significantly reduces pain and joint limitation [10–17]. The present study confirms that treatment with this HA resulted in clinical improvement similar to that of steroid treatment but with longer-lasting effects. These findings are consistent with the results of a previous comparative study between HA and triamcinolone hexacetonide (TH) [12], in which a similar short-term benefit for TH and HA but a longer course of action of HA have been shown.

Arthroscopic studies suggested that this HA is able to reduce the grade and extent of cartilage damage in OA [18, 19] and to slow down radiological joint space narrowing in a subgroup of patients with less advanced OA [20]. In our previous

arthroscopic study [18], we observed that this HA treatment resulted in an improvement in the inflammatory status of the synovial membrane, with a reduction in the numbers of infiltrating mononuclear cells and in the extent of synoviocyte hyperplasia. Furthermore, application of the Mankin score (a combined score assessing structure, cellular abnormalities, matrix staining and tidemark integrity) to quantify microscopic cartilage damage showed that this HA fostered the repair process in the cartilage and the recovery of anabolic activities of surviving chondrocytes, as inferred from the increased affinity of tissue for proteoglycan-specific stains.

The present study further supports the structure-modifying effects of HA of 500–730 kDa. This HA was superior to MP in reducing some of the inflammatory changes affecting the synovial membrane of patients with OA and in delaying structural progression of the disease, particularly in the medial tibial plateau and in the patella compartments. The arthroscopic findings reported here are also in agreement with results of histomorphological examinations of synovial membrane and cartilage from the same study, reported elsewhere [32, 33].

At the synovial level, this HA significantly modified the structural organization reducing the number and aggregation of lining synoviocytes (typical abnormalities of OA), promoting a shift towards normality in shape, internal organization and arrangement of lining cells, reducing the inflammatory pictures and enhancing the repair process in an extent similar to that of MP [32]. Some of these ultrastructural changes were more evident after treatment with HA in primary than in secondary OA.

Concerning the cartilage analysis, after treatment with this HA, there was a significant structural reconstitution of the superficial amorphous layer accompanied by an improvement of the metabolic activity of the chondrocytes, as indicated by the cellular volume occupied by the Golgi, rough endoplasmic reticulum mitochondria [33].

In conclusion, this controlled comparative study suggest that intra-articular hyaluronic acid of MW 500–730 kDa (Hyalgan) exerts beneficial effects, leading to a reduction of synovial inflammation and a slowing of the cartilage damage progression, thus confirming its validity as an alternative (not only symptomatological but also structural) to intra-articular steroids and NSAIDs in the treatment of OA of the knee.

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