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Original Research Article

Hyaluronic acid alone versus hyaluronic acid associated with adelmidrol for intra-articular treatment of knee osteoarthritis: a long-term follow-up

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ABSTRACT

Background: Hyaluronic acid (HA) has been used for many years for intra-articular treatment of knee osteoarthritis with satisfactory results. HA associated with Adelmidrol – an anti-neuroinflammatory compound – have been only recently introduced in orthopedic clinical practice with good preliminary results.

Objective: To investigate whether HA associated with Adelmidrol provides better results than HA alone.

Methods: Two cohorts of patients with moderate knee osteoarthritis were treated. Cohort 1 received 5 weekly intra-articular injections of HA during 2017 while Cohort 2, 4 weekly intra-articular injections of HA associated with Adelmidrol during 2018. The patients of the two Cohorts were assessed by WOMAC scale, SF-12 questionnaire and PGIC scale at 1 week (T0), 6 months (T1), 1 year (T2), and 2 years (T3) after the end of treatment. All the data were statistically analyzed. A p-value of <0.05 was considered statistically significant.

Results: According to the WOMAC Scale, Cohort 1 had higher mean scores than Cohort 2 at each follow-up time, with a statistically significant difference between the two cohorts at T3 ($p<0.03$) for all the WOMAC components, except for Stiffness. WOMAC Total mean score worsened statistically significantly only in Cohort 1, from T1 to T3 (T2 vs T1: $p=0.0033$; T3 vs T2: $p=0.0007$). The same happened for WOMAC Physical Function (T2 vs T1: $p=0.0146$; T3 vs T2: $p=0.0046$) and WOMAC Pain (T2 vs T1: $p=0.0004$; T3 vs T2: $p=0.0002$). WOMAC Stiffness worsened statistically significantly in Cohort 1 from T2 to T3 (T3 vs T2: $p=0.0041$), while in Cohort 2 no change on WOMAC scale was statistically significant at any time-point, for any components. The mean scores of the SF-12 questionnaire were better in Cohort 2 than in Cohort 1 at each follow-up time for both the Physical and the Mental components, with a statistically significant difference between the two groups for the latter, at T0 ($p=0.0001$). In both cohorts the mean score of the Physical component decreased from T0 to T3, but the difference was not statistically significant between the two groups ($p=0.25$). The mean score of the Mental component slightly increased in Cohort 1 and decreased in Cohort 2, without statistically significant differences between the two groups at any time-point. PGIC showed that Cohort 2 scored significantly better than Cohort 1 at T3 ($p=0.0336$).

Conclusions: Overall, HA associated with Adelmidrol gave better long-term results than HA alone.

KEY WORDS: Hyaluronic acid, Adelmidrol, Palmitoylethanolamide, Knee, Osteoarthritis, Synovitis, Mastocytes, Intra-articular injections, Visco-induction.

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INTRODUCTION

Intra-articular injections of hyaluronic acid (HA) are currently used to treat knee osteoarthritis since the first report published in 1971 in the English literature [1].

Recent metanalyses and systematic reviews of the literature have confirmed the clinical efficacy of intra-articular HA injections [2,3].

Adelmidrol is an anti-neuroinflammatory compound that increases the intra-articular level of Palmitoylethanolamide (PEA) that is decreased in inflamed joints [4,5]. PEA in turn modulates mastocytes degranulation, reducing the release of pro-inflammatory factors and lytic enzymes into the joint cavity [6-10]. The rationale for injecting Adelmidrol into an osteoarthritic joint is the presence of many mastocytes within the inflammatory infiltrate of osteoarthritic synovitis [8-12].

The EPITECH GROUP SPA (Saccolongo – Italy) first realized a preparation containing both HA and Adelmidrol. The new preparation was first tested in animals' experimental knee osteoarthritis with good results shown by histopathologic studies [13,14]. Subsequent trials in humans' knee osteoarthritis have shown good clinical results as well [15,16]. However, no comparative study with other intra-articular pharmacologic preparations has been so far carried out.

The aim of the present study was to investigate whether in patients with knee osteoarthritis, the intra-articular injections of the association of a high molecular weight (HMW) HA with Adelmidrol could provide better results than HA of a lower molecular weight injected alone. The results of our study showed that patients treated with the new preparation fared better than those treated with HA alone.

METHODS

Two cohorts of patients with Kellgren-Lawrence unilateral grade II-III knee osteoarthritis [17] were treated at the Department of Physical Therapy and Rehabilitation of Sant'Andrea hospital of the University of Rome "Sapienza", Italy. Cohort 1, including 59 patients, was treated during year 2017 by 5 weekly intra-articular injections of hyaluronic acid with a molecular weight ranging from 0.5 to 0.73 X 10^6 Dalton (2ml pre-filled syringe containing 20 mg of sodium hyaluronate). Cohort 2, including 47 patients, was treated during year 2018 by 4 weekly intra-articular injections of hyaluronic acid of a molecular weight ranging from 1.3 to 2.0 X 10^6 Dalton associated with Adelmidrol (2ml pre-filled syringe containing 1% hyaluronic acid and 2% Adelmidrol). Demographics and BMI of the patients of the 2 cohorts are reported in Tables 1 and 2. Physical activity, defined as at least 2 hours of either sport or gym activity practiced by the patients every day, is reported in Table 3.

According to the inclusion criteria, at the time of treatment the patients of the 2 cohorts had to be symptomatic for at least 6 months, with a pain level of 20 or more evaluated by WOMAC (Western Ontario and McMaster University Osteoarthritis Index) scale [18]. Any previous treatment with anti-inflammatory or pain medications had to be stopped from at least 2 weeks. All the patients had to have provided their informed consent before starting the study. The exclusion criteria included patients whose age was less than 40 years, patients affected by either rheumatic or systemic evolutive diseases, patients treated with NSAIDs from less than 2 weeks, patients treated with corticosteroids from 3 months or less, patients who had either arthroscopic surgery or intra-articular visco-supplementation from 6 months or less. Patients with mental deterioration, with known allergy to hyaluronic acid and/or to Adelmidrol or patients denying their informed consent were also excluded.

Patients of both cohorts were assessed 1 week (T0), 6 months (T1), 1 year (T2), and 2 years (T3) after the last intra-articular injection. Every patient underwent the following evaluation: 1) Anamnestic evaluation regarding BMI, co-morbidities and physical activity; 2) Evaluation of the symptoms and signs typical of knee osteoarthritis as pain, stiffness and functional limitation by the WOMAC scale [18]; 3) Evaluation of the quality of life by the SF-12 (12-Item-Short Form Health Survey)

questionnaire [19]; 4) Subjective evaluation of every patient on her/his improved/worsened clinical status by the PGIC (Patient Global Impression of Change) scale [20]; 5) Radiographic evaluation to assess the Kellgren and Lawrence knee osteoarthritic grade compared to grade II-III present when the treatment was started.

All the data were analyzed according to GLMM (Generalized Linear Mixed Model), that considers patient as the random factor, patient's age, sex, BMI, and physical activity as covariates, and the efficacy of treatment at follow-up as the main effect. The inclusion of the covariates guarantees that the efficacy of treatment is evaluated independently from the influence of the covariates themselves. Post hoc analysis was performed using the Tukey Kramer test adjustment for multiple comparisons. The level of statistical significance has been fixed to $p<0.05$.

RESULTS

No statistically significant difference was found between the 2 cohorts for gender distribution and patients' age (p=0.31; p=0.74; respectively). The difference between the 2 cohorts was statistically significant for BMI (p=0.0030) and physical activity at T0, T1 and T3 (p=0.0001 at T0; p=0.0203 at T1; p=0.11 at T2 and p=0.0188 at T3).

In Cohort 2, all the components of the WOMAC Scale as well as the WOMAC Total had a lower mean score than that of Cohort 1 at each follow-up time, and the difference was significant at T3 for Pain (p=0.0179), Physical Function (p=0.0298), and WOMAC Total (p=0.0191) scores (Fig. 1). In both cohorts, the mean score of all the components of the WOMAC Scale decreased not significantly from T0 to T1 and thereafter increased from T1 to T3. This increase was statistically significant only in Cohort 1, for Pain (T2 vs T1: p=0.0004; T3 vs T2: p=0.0002), Physical Function (T2 vs T1: p=0.0146; T3 vs T2: p=0.0046) and WOMAC Total (T2 vs T1: p=0.0033; T3 vs T2: p=0.0007) scores, while mean WOMAC Stiffness score significantly worsened in Cohort 1 only from T2 to T3 (T3 vs T2: p=0.0041). The mean score of all the components of the WOMAC Scale was not statistically significantly changed in Cohort 2 within the same follow-up intervals. The mean scores of WOMAC Stiffness were adjusted for gender: female had a significantly higher score than male of an average of 0.5 points (p=0.0349). The mean scores of both Physical Function and Total WOMAC were also adjusted for BMI: the increase of one point of BMI significantly increased the score of an average of 0.4 and 0.5 points respectively (p=0.0315 and p=0.0487).

Table 1: Demographic data of the two Cohorts' patients

Patients' number and gender		
	Cohort 1	Cohort 2
Total	59	47
Female	41	28
Male	18	19
Patients' age		
	Cohort 1	Cohort 2
Minimum	42	45
Maximum	83	87
Mean	64,3	65,0
Standard Deviation	12,0	10,5

Table 2: Patients' BMI (Body Mass Index).

Patients' BMI (Body Mass Index)		
	Cohort 1	Cohort 2
Mininimum	19,5	20
Maximum	45,8	34,6
Mean	28,5	25,8
Standard Deviation	5,3	3,5

Both the Physical and Mental components of the SF-12 questionnaire had a lower mean score in Cohort 1 than in Cohort 2 at each follow-up time, but the difference was statistically significant only at T0, for the Mental component alone (p=0.0001). The mean score of the Physical component of the SF-12 questionnaire decreased from T0 to T3 in both cohorts, but the difference was not statistically significant between the two groups (p=0.25). The mean score of the Mental component slightly increased in Cohort 1 and decreased in Cohort 2 from T0 to T3, but the difference was not statistically significant between the two groups at any time-point after T0. Mean scores of the Physical component were adjusted for both gender and physical activity: female scored significantly lower than male of an average of 3.9 points (p=0.0069), and physical activity increased the score of a mean of 2.0 points (p=0.0398).

Table 3: Number of patients involved in physical activity with relative percentage at each follow-up time.

Number of patients involved in physical activity and relative percentage at each follow-up time				
	1 week (T0)	6 months (T1)	1 year (T2)	2 years (T3)
Cohort 1	14	24	25	20
	24%	41%	42%	34%
Cohort 2	29	30	28	27
	62%	64%	60%	55%

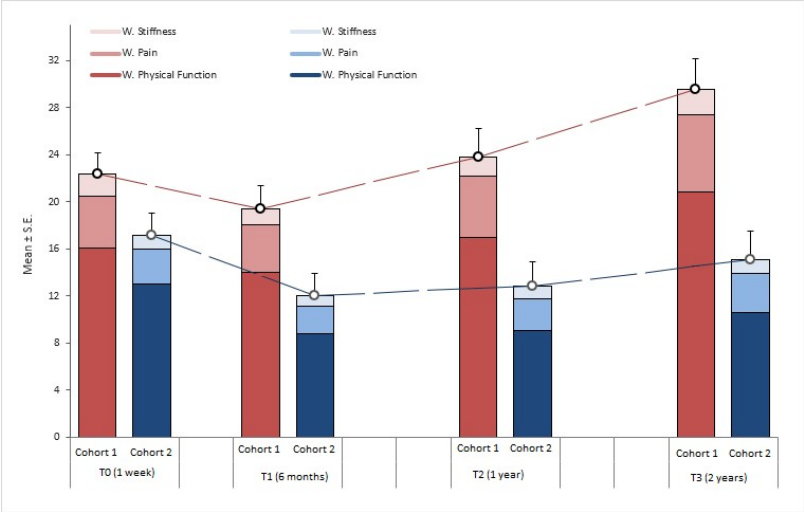

Fig. 1: In Cohort 2, all the components of the WOMAC Scale had a better mean score than that of Cohort 1 at each follow-up time, with a statistically significant difference at T3 for Pain (p=0.0179), Physical Function (p=0.0298) and WOMAC Total (p=0.0191). Mean WOMAC scores significantly worsened in Cohort 1 from T1 to T3 for Pain (T2 vs T1: p=0.0004; T3 vs T2: p=0.0002), Physical Function (T2 vs T1: p=0.0146; T3 vs T2: p=0.0046) and WOMAC Total (T2 vs T1: p=0.0033; T3 vs T2: p=0.0007), while mean Stiffness score significantly worsened only from T2 to T3 (T3 vs T2: p=0.0041). No significative change was present over time in Cohort 2. (W. Stiffness: WOMAC Stiffness; W. Pain: WOMAC Pain; W. Physical Function: WOMAC Physical Function).

Table 4: Patients' percentage of each Cohort with their PGIC score at each follow-up time and statistical difference between the two Cohorts.

Patients' percentage of each Cohort with their PGIC score at each follow-up time						
PGIC Score	**6 months (T1)**		**1 year (T2)**		**2 year (T3)**	
	Cohort 1	**Cohort 2**	**Cohort 1**	**Cohort 2**	**Cohort 1**	**Cohort 2**
	% of patients	**% of patients**	**% of patients**	**% of patients**	**% of patients**	**% of patients**
3	24%	31%	20%	33%	17%	32%
2	49%	47%	32%	35%	17%	27%
1	20%	13%	27%	9%	19%	7%
0	7%	9%	8%	14%	20%	14%
-1			10%	5%	15%	5%
-2			2%	2%	12%	9%
-3			0%	2%	0%	7%
Statistical difference between the two Cohorts						
	6 months (T1)		**1 year (T2)**		**2 year (T3)**	
p value	p=0.69		p=0.14		p=0.0336	

PGIC did not show significant differences between the 2 cohorts at T1 and T2 (p=0.69 and p=0.14 respectively), but the difference was significant at T3 (p=0.03) (Table 4).

No change of the Kellgren and Lawrence grade was evident comparing the knee radiographs of patients in both groups performed at the beginning of treatment with those taken at the last follow-up 2 years later (T3).

DISCUSSION

Patients of Cohort 2 were treated with an association of high molecular weight (HMW) HA and Adelmidrol. These 2 components carry

out a synergic therapeutic action. The former binds to the CD44 receptors present on the plasma membrane of both synoviocytes beta and articular chondrocytes [21,22],

stimulating the synthesis of endogenous hyaluronic acid that is decreased and/or degraded in knee osteoarthritis [23,24]. This mechanism has been defined visco-induction [25]. A normal concentration of HA into the joint cavity is of paramount importance to guarantee articular cartilage lubrication and reduce friction during joint motion [26].

Adelmidrol is the diethanolamide derivative of azelaic acid, and it acts as an anti-neuroin flammatory compound. It increases the endogenous level of PEA that in turn modulates degranulation of mastocytes [27] that are an important component of the inflammatory synovial infiltrate [8-12].

By modulating mastocytes degranulation, Adelmidrol avoids the intra-articular release of several pro-inflammatory factors like nerve growth factor (NGF), interleuchin-beta-1 and tumor necrosis factor (TNF) [28-30] as well as of several enzymes like hexosaminidase able to degrade hyaluronic acid [31-34].

As far as we know, this is the first time that an anti-inflammatory compound other than corticosteroids is used for intra-articular treatment of osteoarthritis of the knee. Moreover, this is the only comparative study of 2 cohorts of patients with knee osteoarthritis one treated with a traditional HA and the other with an association of HMW HA and Adelmidrol.

Patients of Cohort 1 were treated with HA of a lower molecular weight than that used in Cohort 2 patients, and it mainly acts by increasing the intra-articular level of hyaluronic acid (visco-supplementation) [1].

The 2 cohorts were homogeneous for age and gender, but not for BMI and physical activity. Gender negatively influenced WOMAC Stiffness since female patients had a significantly higher score than male. A lower knee range of motion (ROM) of female in comparison to male patients might be explained by the scarce dedication of females to active exercises to improve knee ROM. BMI had a statistical relevant negative influence on both WOMAC Physical Function and Total WOMAC whereas physical activity and gender significantly influenced the Physical component of SF-12 questionnaire.

All the components of the WOMAC Scale scored better in Cohort 2 than in Cohort 1 at all the follow-up times, with a statistically significant difference at the 2-year follow-up (T3) for all of them - with the exception of Stiffness - showing that the association HMW HA with Adelmidrol was more effective than HA alone in maintaining long term clinical improvement achieved by the patients at the end of infiltrative treatment.

The effectiveness of treatment tended to worsen in time from T0 to T3, significantly from T1 to T3 in Cohort 1 as shown by the WOMAC Scale mean scores, while in Cohort 2 the good results were maintained over time, since not significant difference was observed between the WOMAC Scale mean scores from T0 to T3. Those data show that the good clinical results obtained by the association of HMW HA with Adelmidrol lasted up to the 2-year follow-up (T3) while HA alone showed a statistically significant deterioration of the clinical outcome as early as T1 to T2.

The SF-12 questionnaire showed better mean scores at all the follow-up times in Cohort 2 than in Cohort 1, although the difference was statistically significant only for the Mental component at 1-week follow-up (T0). The mean scores of the Physical component worsened not–significantly in both cohorts while the mean scores of the Mental component slightly worsened in Cohort 2, and slightly likewise not-significantly improved in Cohort 1 from T0 to T3. The different behavior of the Mental component of SF-12 - that expresses the emotional attitude of the patients of the 2 cohorts - is difficult to explain because the patients of Cohort 2 appreciated the result of treatment at each follow-up time as better than those of Cohort 1, but they felt that the maintenance of the positive effect of treatment was decreasing in time while patients of Cohort 1, that had a worse score at each follow-up time, felt that the positive effect of treatment was maintained in the long-term.

That finding is also in contrast with the results of PGIC scale that showed how Cohort 2 patients scored significantly better than that those of Cohort 1 at 2-year-follow-up.

The radiographs of the knee of the patients of both cohorts made at the last 2-year-follow-up did not show any evident modification of the Kellgren and Lawrence grade when compared to the radiographs made before the beginning of treatment. However, it is difficult to say whether the absence of radiographic worsening during the 2-year-follow-up was due to treatment or rather, to the natural history of osteoarthritis.

Numerous studies have reported satisfactory results in patients with knee osteoarthritis treated by intra-articular injections of HA. However, most of those studies have a follow-up either equal or inferior to 3-6 months as reported by a recent metanalysis [35].

Very few studies have a follow-up of 1 year or more, and almost all show deterioration of the results in the long-term like we observed in Cohort 1 [36-38]. To the contrary, our study shows that the association of HMW HA with Adelmidrol provided satisfactory results in a high percentage of cases even at 2 years from the last intra-articular injection. The explanation of this point is speculative in humans. However, the positive therapeutic effect of the new association has been exhaustively demonstrated by histologic studies in animals in which the alterations induced by experimental knee osteoarthritis were fully recovered at the end of treatment [13,14].

Our study has several limitations. First, it is a retrospective study of 2 cohorts of patients treated with 1 year interval from each other. Consequently, the treatment of the 2 cohorts could not be randomized. Second, the 2 cohorts were not fully homogeneous because there was a statistically significant difference between them for both BMI and physical activity. Third, the lack of randomization makes the results only valid for the patients of the 2 cohorts, and thus not extendable to the general population. Further randomized studies will be needed to confirm the results obtained in the present study.

CONCLUSION

In conclusion, according to the 3 evaluation scales adopted by us, the patients of Cohort 2 had an overall better result than those of Cohort 1 at any follow-up time from T0 to T3 and, for some parameters, the results were significantly different at the 2-years follow-up. The objective data were also strengthened by the subjective evaluation of the patients assessed by the PGIC scale that showed a significantly better score of the patients of Cohort 2 in comparison to those of Cohort 1 at 2-year-follow-up. We might speculate that the best therapeutic effect of the association of HMW HA with Adelmidrol has developed in the short-term by the prevalent anti-neuroinflammatory effect of Adelmidrol while, in the long-term, by the visco-inductive effect of HMW HA. However, further experimental studies will be needed to better clarify this point.

ABBREVIATIONS

HA - Hyaluronic Acid
ROM - Range of Motion
HMW - High molecular weight
BMI - Body Mass Index

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