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ORIGINAL ARTICLE

Patient-reported outcomes of intra-articular hyaluronic acid for osteoarthritis of the knee: a prospective and multicentric case series

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Abstract

Background In the present study, patients with symptomatic knee osteoarthritis (OA) were treated with single intra-articular injection of a high molecular weight, non-cross-linked hyaluronic acid (HA), highly concentrated (2%) and associated with sorbitol (4%). The aims of this study were to (1) evaluate clinical outcome after 6 months, (2) evaluate clinical outcomes after 12 months and (3) evaluate clinical outcomes according to OA grade. Hypothesis of the study was that a single intra-articular injection of this HA associated with sorbitol leads to a significant clinical improvement within 6 months in patients with early or moderate knee OA.

Materials and methods A total of 77 patients were enrolled in this prospective multicentric study. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score was recorded at baseline and at months 1, 3, 6 and 12 following the intra-articular injection. Moreover, a stratified analysis of all WOMAC items following the OA grade was performed for both groups of patients, one with low (grade I–II according to Kellgren–Lawrence classification) and another with moderate OA grade (grade III according to Kellgren–Lawrence) and the differences between groups were evaluated.

Results Seventy-three patients completed the 12 months follow-up. Pain, stiffness, functional limitation and total scores were significantly reduced at 1, 3 and 6 months ($p < 0.05$), but not at 12 months. Stratified analysis of all subscores according to OA grade showed that pain, functional limitation and total score decreased at 1, 3, 6 and 12 months ($p < 0.05$) in both groups. Stiffness was the only item that decreased significantly at 1, 3 and 6 months but not at 12 months in both groups. All subscore values were significantly lower in the group of patients with low OA grade compared to the one with moderate OA grade. No adverse events were reported.

Conclusion At 6 months after a single intra-articular injection of a high molecular weight, non-cross-linked HA associated with sorbitol, WOMAC scores decreased significantly. Clinical benefits were observed both in patients with low and in those with moderate OA grade, with better results in the first group.

Keywords Osteoarthritis · Knee · Viscosupplemantation · Hyaluronic acid · Intra-articular injection · Patient-reported outcomes

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Introduction

In adult population, osteoarthritis (OA) is the leading cause of disability and is among the leading conditions causing work limitations. Over the next 25 years, the number of people affected and the social impact of doctor-diagnosed arthritis are projected to increase by 40% in the USA. It was also estimated that 242 million people live with symptoms caused by OA of the knee or hip [1].

OA of the knee is due in part to a decreased viscosity of synovial fluid which normally acts as a cushion. A healthy joint is lubricated with 1–2 mL of synovial fluid containing 5–8 mg of hyaluronic acid (HA). In the arthritic knee, however, the HA content is diminished, reducing the viscoelastic properties of the joint and increasing the stress on the articular surface, causing erosion, bone spurs and pain [2]. Balazs and Denlinger were the first to suggest intra-articular injection of HA use for restoration of viscoelastic properties and improved functionality, and several compounds with differing molecular weight, preparation of purified sodium hyaluronate and injection schedules have since been introduced into clinical practice [3, 4].

Less severe forms of knee OA are commonly managed with intra-articular injection of hyaluronic acid (HA). Though meta-analyses have failed to identify significant clinical changes [5], closer and more recent examinations reveal that viscosupplementation results in clinically important pain reductions [6].

In this prospective, multicentric study, patients with symptomatic knee OA were treated with a single intra-articular injection of a high molecular weight, non-cross-linked hyaluronic acid (HA), highly concentrated (2%) and associated with sorbitol (4%). The aims of this study were: (1) to evaluate clinical outcomes after 6 months, (2) after 12 months and (3) to evaluate clinical outcomes according to OA grade. The hypothesis was that this intra-articular treatment leads to a significant clinical improvement within 6 months in patients with low to moderate grades of knee OA.

Materials and methods

Study subjects

Three groups in different institutes across Italy were involved in the present study. Seventy-seven patients were screened and enrolled, of which 73 completed the 12 months follow-up (Flowchart Fig. 1). The inclusion criteria were: (1) patients from 40 to 80 years of age, (2) unilateral knee OA confirmed by X-ray, (3) persistent symptoms within the last 6 months, (4) unresponsive to non-steroidal or steroidal anti-inflammatory medication and (5) no knee injection within 6 months prior to inclusion. Exclusion criteria were: (1) patients mentally uncapable of following the study instructions, (2) patients suffering from rheumatoid arthritis or other rheumatic diseases, (3) osteonecrosis of the knee and (4) pregnant women. Kellgren–Lawrence classification was used to classify OA grade at X-ray examination [7].

Characteristics of the study cohort at baseline are shown in Table 1.

All patients expressed their consent to undergo 4 mL SynolisVA ® 80/160 intra-articular injection and to be prospectively evaluated. SynolisVA® 80/160 is a high molecular weight (2MDa), non-cross-linked, highly concentrated HA (2%), associated with sorbitol (4%) to improve antioxidant effect.

Study design

In this prospective, multicentric study, patient-reported outcomes (PROMs) were recorded using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [8]. Scores were recorded at baseline and at months 1, 3, 6 and 12 following a single injection of a specific association of HA and sorbitol. WOMAC scores

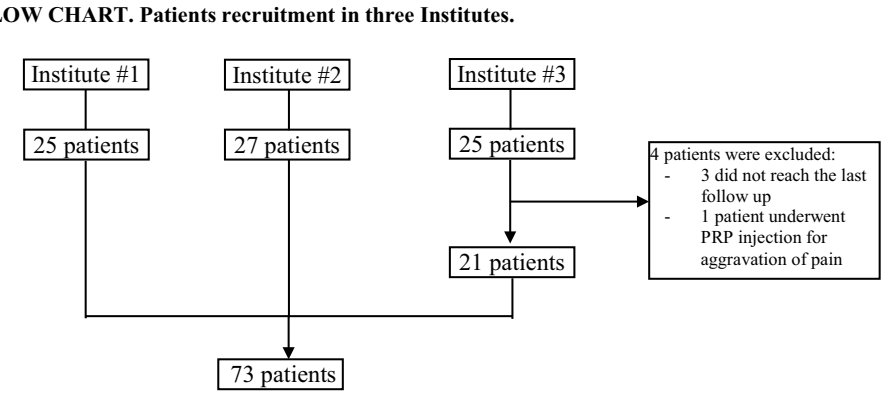

Fig. 1 Patients recruitment in three institutes

Table 1 Demographic data

Patients (n)	73
Men	29
Woman	44
Age years, mean (SD)	57.3 (±13)
BMI, mean (SD)	24.41 (±3.45)
Weight, kg, mean	70.4 (±12.4)
Height, cm, mean (SD)	169.8 (±9.6)
Knee affected	
Right	39
Left	34
Kellgren–Lawrence	
Grade I	2
Grade II	45
Grade III	26
Grade IV	0

are based on five items related to pain (subscore: 0–60; 0 = minimum pain subscore; 60 = maximum pain subscore), two items related to stiffness (subscore 0–16; 0 = minimum stiffness subscore; 16 = maximum stiffness subscore) and 17 items related to physical activity (subscore 0–156; 0 = minimum physical activity subscore; 156 = maximum physical activity subscore). Moreover, a stratified analysis according to Kellgren–Lawrence OA grade was done for all WOMAC items and differences between two groups (Group 1: grade I–II; Group 2: grade III) were evaluated.

Statistical analysis

Items were analyzed using *t* test. A value of $p < 0.05$ was considered statistically significant, and data were represented as the mean ± standard deviation (SD) of the mean. *T* test was used in the stratified analysis according to OA grade. Software STATA (StataCorp, 1985) SPSS v.19.0 was used for all analyses.

Results

No adverse events were reported. Items' values are reported in Table 2.

Table 2 WOMAC score

Follow-up	Items	Min	Max	Mean	SD
0 month	Pain	2.0	50.0	27.6	11.5
	Stiffness	1.0	14.0	5.1	3.0
	Functional limitation	18.0	156.0	77.9	30.7
	Total score	29.0	209.0	112.5	42.1
1 month	Pain	0.0	49.0	20.1	9.9
	Stiffness	0.0	12.0	3.7	2.4
	Functional limitation	0.0	137.0	62.3	29.4
	Total score	0.0	194.0	87.4	38.2
3 months	Pain	2.0	60.0	17.6	10.3
	Stiffness	0.0	10.0	3.3	2.2
	Functional limitation	8.0	132.0	55.9	28
	Total score	13.0	185.0	77.2	36.0
6 months	Pain	3.0	44.0	13.9	8.7
	Stiffness	0.0	12.0	2.9	2.1
	Functional limitation	5.0	120.0	46.5	27.6
	Total score	12.0	176.0	63.3	34.6
12 months	Pain	3.0	50.0	22.3	12.1
	Stiffness	1.0	16.0	6.4	3.7
	Functional limitation	13.0	150.0	57.2	34.1
	Total score	18.0	198.0	85.9	46.2

WOMAC scores within 6 months

Pain, stiffness, functional limitation and total scores were all reduced at months 1, 3 and 6 ($p < 0.05$, Figs. 2, 3, 4 and 5).

WOMAC scores at 12 months

Pain, functional limitation and total scores were lower at 12 months compared to baseline, but these decreases were not significant ($p > 0.05$). Stiffness was the only item where the score increased comparing to pre-injection time.

WOMAC scores stratified by OA grade

Two patient groups were formed according to OA grade: Group 1 (G1), composed of patients with grade I and II (G1 = 47 patients; grade I = 2 patients; grade II = 45 patients); Group 2 (G2), composed of patients with grade III (26 patients). No patient with grade IV was identified.

No difference was found in trends between two groups (Figs. 6, 7, 8 and 9). In fact, in both groups, all items decreased significantly at all follow-up evaluations, except for stiffness at 12 months.

Specific values of all items at all four follow-up evaluations were compared between the two groups (Table 3): There was a significant difference in pain score between G1 and G2 at 3 and 6 months, in stiffness score at 1, 3 and

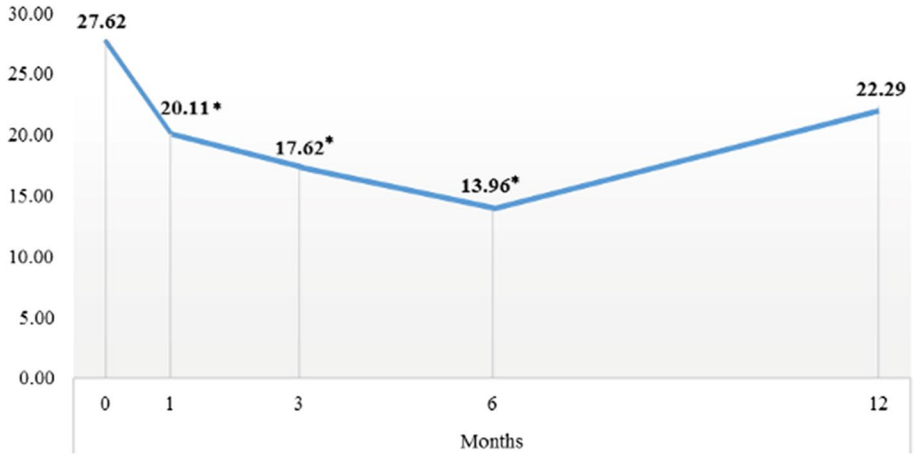

Fig. 2 Trend of pain; *$p < 0.05$

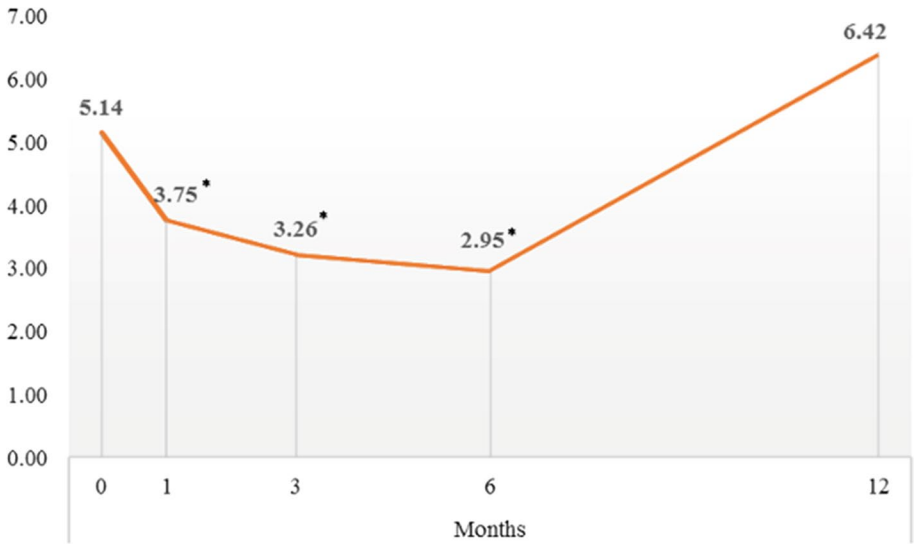

Fig. 3 Trend of stiffness (main); *$p < 0.05$

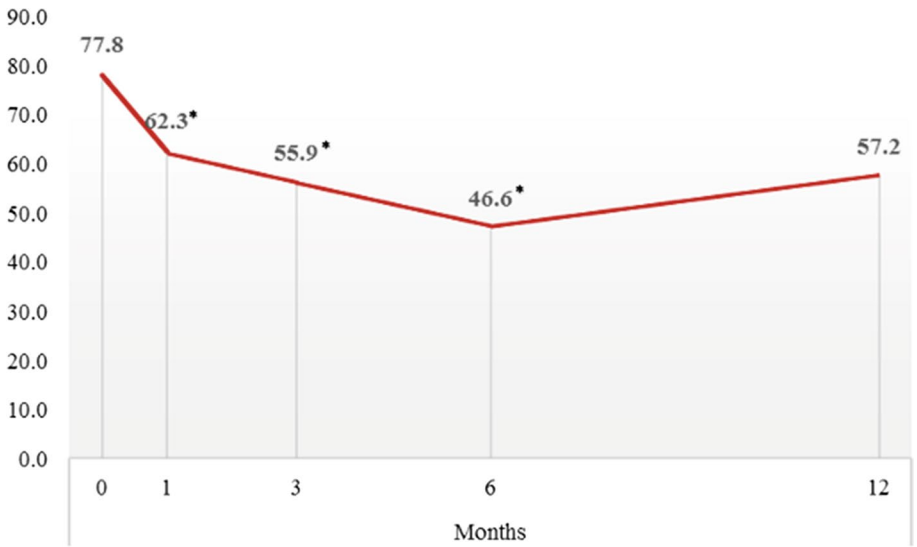

Fig. 4 Trend of functional limitation (main); *$p < 0.05$

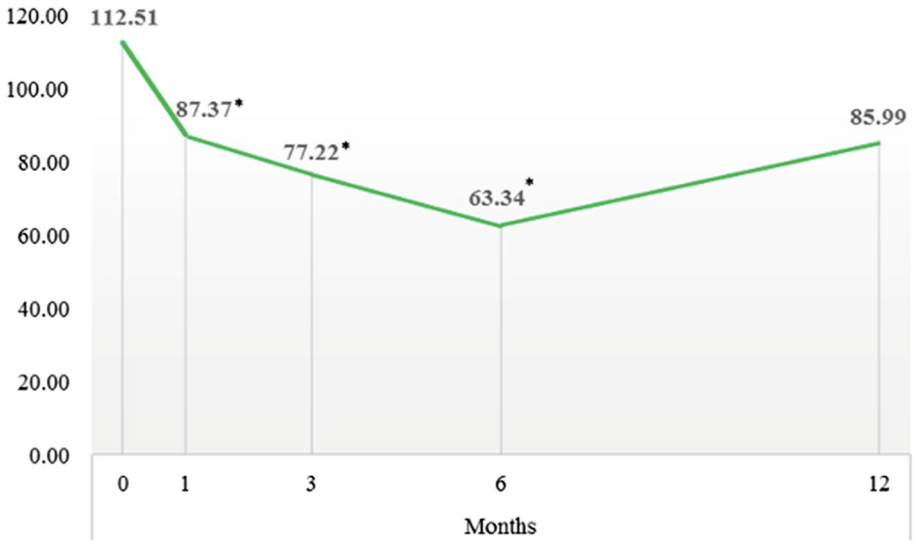

Fig. 5 Trend of total score (main); *$p < 0.05$

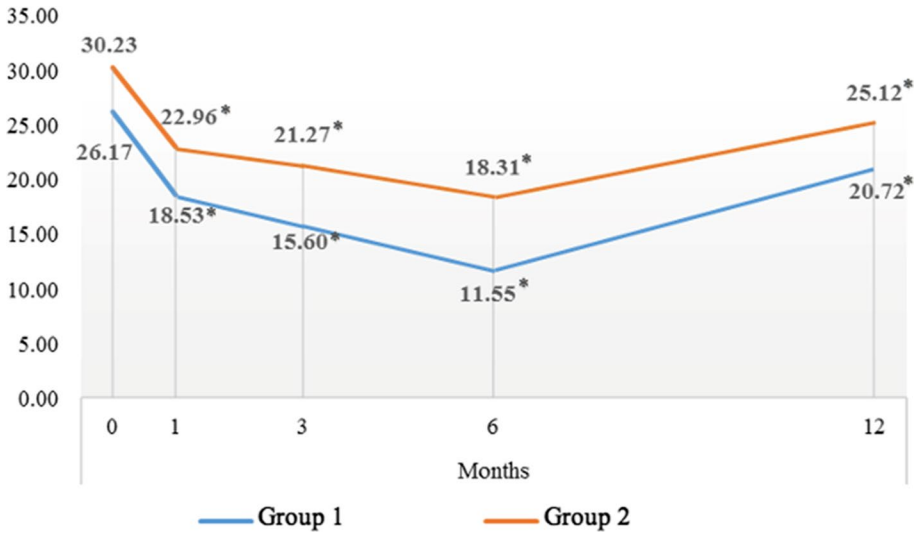

Fig. 6 Trend of score of pain in Group 1 and Group 2; $p < 0.05$

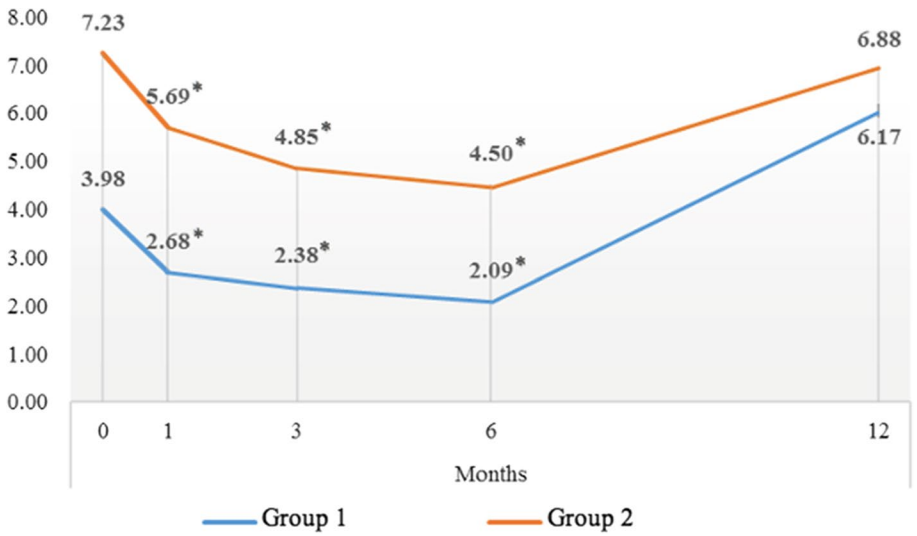

Fig. 7 Trend of score stiffness in Group 1 and Group 2; $p < 0.05$

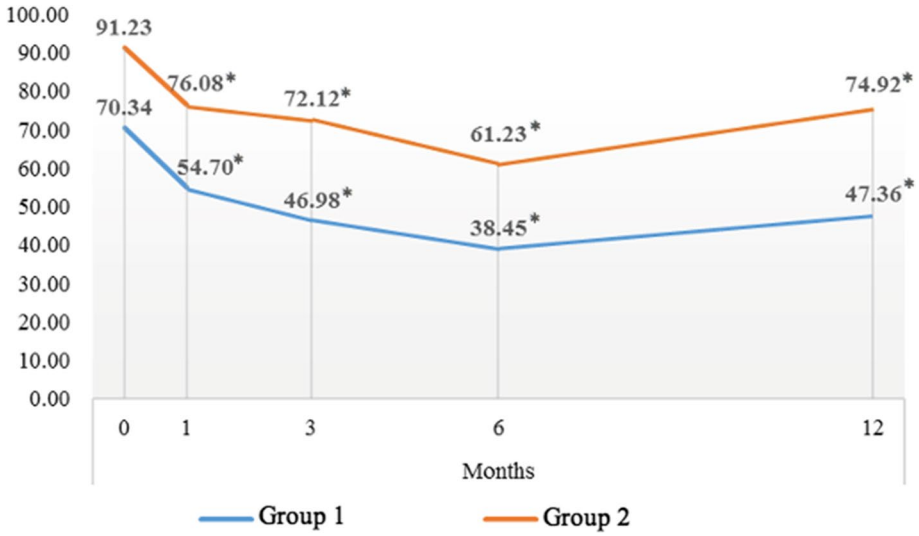

Fig. 8 Trend of score of functional limitation in Group 1 and Group 2; $p < 0.05$

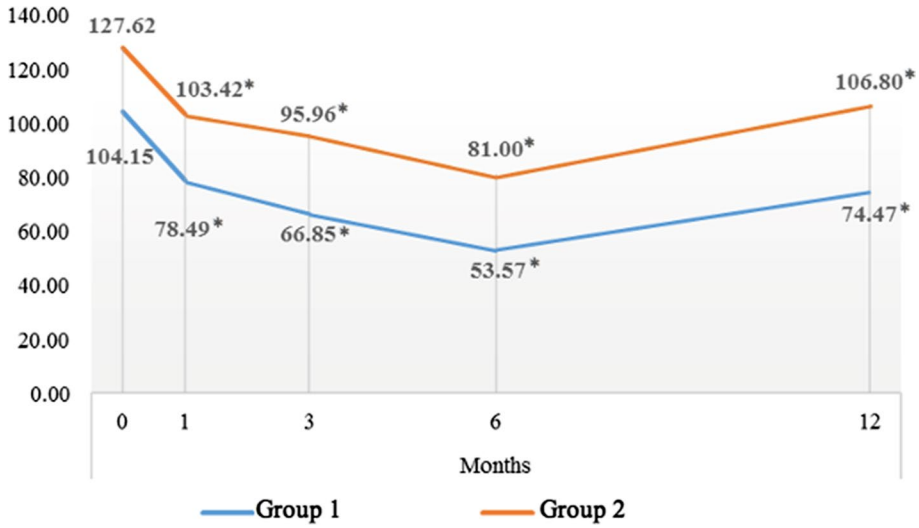

Fig. 9 Trend of score of total score in Group 1 and Group 2; $p < 0.05$

6 months and in functional limitation and total score at all follow-up evaluations.

Discussion

The current study is the first one that demonstrated the efficacy of a single intra-articular injection of a high molecular weight, non-cross-linked hyaluronic acid associated with sorbitol. According to the results, all WOMAC scores decreased significantly throughout the 6 months study period. At 12 months, the scores did increase when compared to 6 months levels but nevertheless remained lower than pre-injection baseline values. This gradual and persistent clinical improvement was also confirmed in the stratified analysis according to OA grade. These two elements demonstrate that significant clinical benefits persist over the 6 months period. This was observed both in patients with low OA grade and in those with moderate OA grade, with better results for the first group.

Recent review suggested that the effects of intra-articular HA injection in reducing pain for knee OA were likely to take place in four to eight weeks and could last up to twenty-four weeks [9]. Our findings suggest that the efficacy of combination of HA and sorbitol is significant and lasted sustainably for 6 months. Moreover, its effects showed to persist up to at least 12 months. However, such effects were found to be more sustainable on pain and physical function than on stiffness which is consistent with the findings of several studies [10, 11].

Similar to previous study [12], this study also demonstrated that intra-articular HA injection was safe regardless of the dosage regimens used. However, we conclude that the single larger dose is preferable to be used routinely in

Table 3 Difference between Group 1 and Group 2

Follow-up	Items	Group 1	Group 2	*p*
1 month	Pain	18.53	22.96	0.06
	Stiffness	2.68	5.69	0.00*
	Functional limitations	54.70	76.08	0.00*
	Total score	78.49	103.42	0.00*
3 months	Pain	15.60	21.27	0.02*
	Stiffness	2.38	4.85	0.00*
	Functional limitations	46.98	72.12	0.00*
	Total score	66.85	95.96	0.00*
6 months	Pain	11.55	18.31	0.00*
	Stiffness	2.09	4.50	0.00*
	Functional limitations	38.45	61.23	0.00*
	Total score	53.57	81.00	0.00*
12 months	Pain	20.72	25.12	0.16
	Stiffness	6.17	6.88	0.38
	Functional limitations	47.36	74.92	0.00*
	Total score	74.47	106.80	0.01*

*$p < 0.05$

the future, as it is generally more convenient and acceptable for the patients [13, 14]. Besides, it potentially reduces the risks of complications at the injection site, patient's anxiety or fear of the procedure and hospital surcharge.

By aggregating the evidence into systematic reviews, meta-analyses, network meta-analyses and guidelines, a message begins to emerge but remains difficult to fully understand because of conflicting results and poor methodological quality of clinical trials [15]. A careful examination of the most recently published articles suggests that viscosupplementation is a safe option with a clinically important reduction in pain especially in younger patients with knee OA when used in formulations with higher molecular weights or HA cross-linking.

Here, we can state that patients reported an improved clinical condition at 12 months compared to baseline, even though those values did not reach statistical significance in the cohort analysis.

The only exception was stiffness: This item, in fact, got worse at 12 months. This result could be the consequence of progressive increase in mobility due to reduction in pain and physical limitation during the previous months.

Consistent with recent guidelines of international societies [9–11], our study confirms the validity of the treatment with injectable HA in patients suffering from OA of the knee, in particular, during the early stages of this pathology.

It is interesting to stress that only a single injection was administered which improved patient's compliance and reduced infection risk.

Another positive result was the absence of adverse effects.

Conclusion

High molecular weight, non-cross-linked, highly concentrated hyaluronic acid (2%) associated with sorbitol (4%) is a valid and safe option for knee OA treatment. Authors recommend this association in the early stage, with low to moderate grades of OA. Patients reported significant clinical improvement from the first month, and this result persisted for at least 6 months.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest regarding the publication of this paper.

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