International Orthopaedics (2019) 43:2437–2445
https://doi.org/10.1007/s00264-019-04360-8

ORIGINAL PAPER

Prevention of post-traumatic osteoarthritis after intra-articular knee fractures using hyaluronic acid: a randomized prospective pilot study

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Received: 13 August 2018 / Accepted: 12 June 2019 / Published online: 22 June 2019

Abstract

Purpose Based on the irreversible destruction of hyaline cartilage, post-traumatic osteoarthritis (PTOA) is a notorious sequelae after intra-articular knee fractures. This study evaluates the clinical efficacy and applicability of immediate post-operative intra-articular injection of hyaluronic acid (IA HA) into the knee joint with an intra-articular fracture.

Methods Prospective randomized case-control study involving 40 patients (20 in each group) with intra-articular knee fracture with an average follow-up of 23 months (range 18–24 months). Twenty patients with intra-articular distal femoral or intra-articular proximal tibial fractures who met our inclusion criteria received three intra-articular hyaluronic acid injections weekly starting immediately after ORIF. Another 20 patients serving as a control group received no injection after ORIF. Patients were assessed functionally with Knee injury and Osteoarthritis Outcome Score (KOOS) and International Knee Documentation Committee (IKDC) score. Plain X-rays and when indicated CT scans were used to assess radiological union.

Results The results showed patients treated with intra-articular hyaluronic acid injection after fixation had significantly less pain (KOOS) ($p = 0.01$). No significant difference was found between both groups in other KOOS-related outcome measures, complications, functional outcome, or quality of life.

Conclusions These preliminary results support a direct role for hyaluronic acid in the acute phase of the inflammatory process that follows articular injury and provides initial evidence for the efficacy of IA HA.

Keywords Intra-articular injection after trauma · Intra-articular hyaluronic acid injection · Hyaluronic acid (HA) · Post-traumatic osteoarthritis

Introduction

With the current best care of major joint injuries, the risk of post-traumatic OA (PTOA) ranges from 20% to more than 50%. Particularly in intra-articular knee injuries, PTOA irrevocable destruction of hyaline cartilage has been reported to occur in more than 40% [1]. Thus, preventing the initiation of post-traumatic osteoarthritis has become an area of intense research. Direct intra-articular injection in the early phase after joint injury poses an attractive modality as it allows for high local drug concentrations and avoids opposing systemic adverse effects such as allergic reactions [2].

Level of evidence Level 2

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Mechanisms responsible for post-traumatic osteoarthritis

Acute structural damage occurring at the time of the injury and gradual-onset structural damage due to the abnormal load distribution constitute the mechanical foundation for PTOA [3, 4]. Furthermore, an acute inflammatory reaction concerted by the release of inflammatory mediators such as TNF, metalloproteinases, aggrecanases, and nitric oxide leads to cartilage cell necrosis and apoptosis [5, 6].

Therefore, acute therapeutic intervention after intra-articular injury should prove useful and effective in inhibiting or decreasing the pro-inflammatory effect induced by

cytokines making intra-articular injections a valid and effective option [4].

Dexamethasone, BMP-7 (bone morphogenetic protein 7), hyaluronic acid (HA), z-VAD-fmk, and N-acetylcysteine have been proposed to preserve chondrocytes and prevent injury-induced proteoglycan losses [5, 7, 8].

Being a long-chain biopolymer composed of repetitive molecular sequences of N-acetyl-glucosamine and glucuronic acid, HA serves in joint cartilage as the support for proteoglycans. Chondrocytes are embedded in a matrix consisting of collagen and HA. The latter serves also as a coating for the joint cartilage and synovial membrane and provides shock-absorbing capability to the joint fluid [9].

HA restores viscoelastic properties such as lubrication, elasticity, and joint cushioning (viscosupplementation) and furthermore restores joint rheology, has anti-inflammatory and anti-nociceptive effects, normalizes endogenous hyaluronic acid synthesis, and favors chondroprotection (biosupplementation) [10, 11]. This occurs through the inhibition of immune complex adherence to polymorphonuclear cells, the inhibition of leukocyte and macrophage migration and aggregation, fibroblast growth, and scavenging of free radicals [11].

These mechanisms explain focal cartilage damage, but they cannot sufficiently explain the whole joint arthritis which often sets in after initial focal cartilage injury. To date, there are no approved therapeutic interventions in clinical use that can avoid or decrease the development of PTOA after IA fractures [12].

Adverse effects of intra-articular injections are numerous and may include infection, further mechanical and chemical cartilage damage, granulomatous synovitis, allergic reactions, and systemic side effects [7]. Therefore some authors do not recommend more than one injection while most others stringently avoid IA injections in the acute trauma setting [7, 13].

Medicinal hyaluronic acid is extracted from rooster combs or produced by bacteria in the laboratory [14]. Intra-articular hyaluronic acid injection is a known but disputed remedy for knee OA that reportedly provides numerous biochemical and biological benefits, including shock absorption, chondroprotection, and anti-inflammatory effects within the knee [15].

This study intends to reveal the efficacy of acutely applied IA HA in intra-articular knee fractures involving distal femoral and proximal tibial articular surfaces regarding pain, functional outcomes, bony union, and possible complications.

Patients and methods

After receiving ethical board approval, this prospective randomized case control study was conducted at Orthopedic Department, Cairo University in the period from November 2015 to December 2017, albeit this study is ongoing with an intended final follow-up of 48 months, to conceivably reveal the early onset of osteoarthritis. All patients signed an informed and detailed consent describing the procedure and possible complications. Only patients who provided written informed consent were enrolled in this study. Three patients refused IA HA and were excluded from the start (Fig. 1).

Forty patients with intra-articular knee fracture were treated with a total average follow-up of 23 months (range 18–24 months). All consecutive patients presenting to our emergency department in the abovementioned time span with an intra-articular knee fracture who met the inclusion criteria were asked to participate in this study. Simple randomization was achieved by a computer-generated random number. Twenty patients were injected with intra-articular hyaluronic acid after ORIF (group A) and 20 patients received no injections after ORIF serving as a control group (group B). Group A patients received three injections at a weekly interval starting immediately after surgery. The employed prefilled hyaluronic acid syringe consisted of Hyalgan® (Fidia Pharma USA Inc., Parsippany, NJ, USA), a viscous solution consisting of a high molecular weight (500,000–730,000 Da) fraction of purified natural sodium hyaluronate in buffered physiological sodium chloride. Two milliliters of Hyalgan® was applied three times by the first author in the suprapatellar bursa strictly under aseptic conditions at weekly intervals. For fear of infection, control group B received no placebo IA injections. Indeed, the absence of a "true" placebo group weakens this study validity significantly due to attributable psychological effects. Hence this study could be considered a pilot study for further multicentric efforts.

Inclusion criteria included age from 18 to 45 years, distal femur and proximal tibia type B knee partial articular fractures

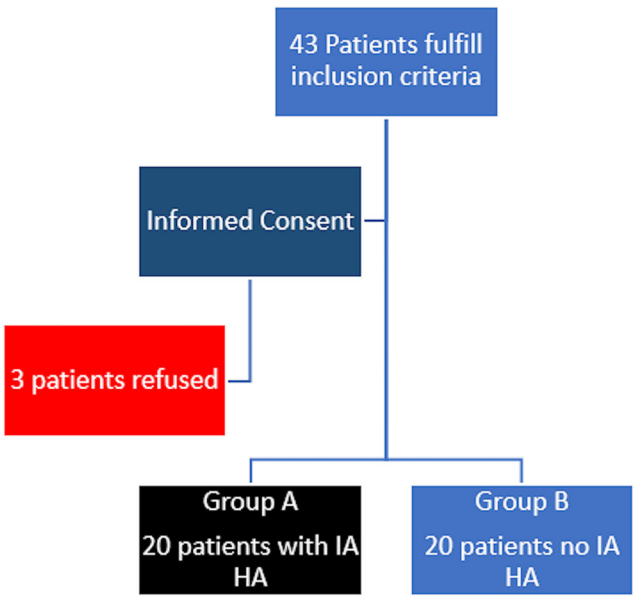

Fig. 1 Study flowchart

(B1, B2 pure depression, B3 split depression), and type C complete articular fractures (C1 articular simple, metaphyseal simple, C2 articular simple, metaphyseal multifragmentary) according to the AO classification.

Exclusion criteria were open fractures, extra-articular fractures and multifragmentary intra-articular type C3 fractures, diabetes mellitus, and immune suppression.

Patients who met the inclusion criteria were randomly divided into two groups.

In group A, the mean age was 33.6 years (range 21 to 41 years) while in group B, the mean age was 34.3 years (range 20 to 44 years). In group A, there were 75% males and 25% females, while in group B, there were 60% males and 40% females.

Fractures were classified according to the AO classification, and in group A, there were 16 patients with proximal tibial fractures and 4 with distal femoral fractures. In group B, there were 17 patients with proximal tibial fractures and three with distal femoral fractures **(**Table 1**).**

Internal fixation was done within zero to seven days from trauma, depending on the soft tissue envelope condition. Meanwhile, all patients were put in an above knee splint. To minimize the surgical variance, all surgery was performed by the senior author who has 30 years of orthopaedic trauma surgery experience. Ceftriaxone 2 g IV was given half an hour pre-operatively. All patients received general or spinal anaesthesia. They were placed in a supine position with the knee semi-flexed on a radiolucent table. The C-arm was placed contralaterally to the injured extremity, and the tourniquet was elevated to 100 mmHg above systolic pressure. The anterolateral approach was chosen in lateral tibial condylar fractures, the anteromedial approach in medial tibial condylar fractures, and the lateral approach in intercondylar femur fractures. ORIF was accomplished according to the fracture geometry with anatomical locked plates and/or screws. After skin closure, patients of group A received the first injection of 2 ml Hyalgan® through a sterile prefilled syringe in the suprapatellar bursa as the latter communicates freely with the joint cavity (Fig. 2).

Table 1 Distribution according to type of fracture

Type of fracture			Frequency	Percent
Group A	Proximal tibia	(AO 41-B1)	5	25
		(AO 41-B3)	3	15
		(AO 41-C1)	4	20
		(AO 41-C2)	4	20
	Distal femur	(AO 33-C1)	2	10
		(AO 33-C2)	2	10
Group B	Proximal tibia	(AO 41-B1)	4	20
		(AO 41-B3)	4	20
		(AO 41-C1)	6	30
		(AO 41-C2)	3	15
	Distal femur	(AO 33-C1)	2	10
		(AO 33-C2)	1	5

Post-operative management and follow-up

Post-operatively, isometric quadriceps strengthening exercises for 6 weeks were started and active range of movement exercises up to 90° flexion were allowed on the third and fourth days. The patients were mobilized non-weight bearing after removal of the strictly extra-articular non-suction drain using a walking frame for six weeks. Weight bearing was allowed between six and 12 weeks after surgery, progressing from partial weight bearing after six weeks till full weight bearing after 12 weeks after achieving clinical and radiological union.

In the first and second post-operative week, the patients received their second and third dose of Hyalgan® in the outpatient clinic, respectively, and at the sixth week, radiological and range of motion follow-up was done. At six months and 12 months, another functional and radiological control was

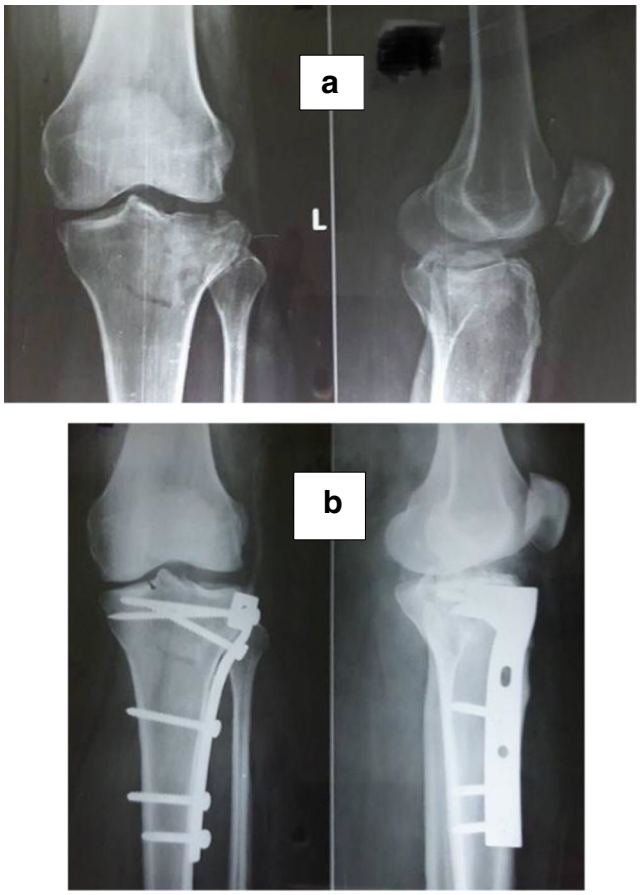

Fig. 2 A 30-year-old male patient following road traffic accident with right tibial plateau fracture type AO 41-B3.1 (**a**). After ORIF with anatomical proximal tibial plateau locking plate, he received IA HA, and at final follow-up at 24 months, he had a full knee extension and flexion range of motion (0–135°) (**b**)

done, and at 18 months, the KOOS scores [16] and IKDC scores [17] were appraised. Both KOOS and IKDC in addition to time to full weight bearing and radiological union were considered outcome criteria. KOOS scores of the five dimensions were assessed separately; an aggregate score was not calculated as it was regarded desirable to analyze and interpret its five dimensions separately (Fig. 3).

Statistical methods

After anonymizing the data, it was analyzed using SPSS version 23 (IBM, Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum, and maximum for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using unpaired *t* test. Comparison between KOOS and IKDC scores with injection and without injection groups was done using paired *t* test.

Chi-square (χ^2) test was performed for comparing categorical data. Exact test was used instead when the expected frequency was less than 5. *p* values less than 0.05 were considered statistically significant. Multivariate analysis of variance (MANOVA) with post hoc testing was performed to disclose how independent variables influence patterns of response on the dependent variables.

Results

Clinical

Comparing the time to full weight bearing in weeks, there was no statistical significance as the *p* value was 0.307 with a mean of 14.31 weeks (range 12–18 weeks) in group A and 14.94 weeks in group B (range 12–18 weeks) **(**Table 2**)**.

Post-operative hospital stays averaged five days and varied from four to six days without a significant difference between group A and group B.

The Knee injury and Osteoarthritis Outcome Score (KOOS) was assessed separately at 18 months post-operatively in its five dimensions including other symptoms, knee pain, function of daily living, sport and recreational activities, and quality of life (QOL). The intended overall follow-up is 48 months as 18 months of follow-up will most likely not reveal significant trauma-associated OA, and therefore this study should be considered a preliminary report. Only pain was statistically significant (*p* value = 0.001) when comparing group A and group B at 18 months post-operatively. The other dimensions showed no statistical significance (Table 3). Similarly, the International Knee Documentation Committee (IKDC) scores at 18-month follow-up among both groups were also statistically insignificant (*p* value 0.718) (Table 4).

In group A, time to full radiological union averaged 14.63 months compared with 14.72 months in group B indicating no statistical significance (*p* value = 0.998) **(**Table 5**).**

Dependent variables were examined for normal distribution prior to MANOVA testing. A one-way MANOVA revealed a significant multivariate main effect for HA injections, Wilks' $\lambda = 0.386$, $F\ (9, 23.00) = 4.074$, $p < 0.003$, and partial $\lambda^2 = 0.614$. Power to detect the effect was 0.968. Given the significance of the overall test, the univariate main effects were examined. Significant univariate main effects for KOOS pain were obtained for HA injections, $F\ (1, 31) = 22.50$, $p < 0.001$, partial $\lambda^2 = 0.421$, and observed power = 0.996. Gender and fracture site, either proximal tibial or distal femoral, had no effect on the dependent outcome variables (Table 6).

With Cohen's effect size *d* set to 0.8 and a sample size of 20 patients in each group, further post hoc power analysis revealed a power of $1 - \beta$ err = 0.799 qualifying this work as a pilot study.

Complication

Injection-related complications such as allergy, pruritus, joint pain, or pain at the injection site were not encountered in group A. Infection occurred in two (10%) in group A patients and in four (20%) group B patients. In group A, single-staged

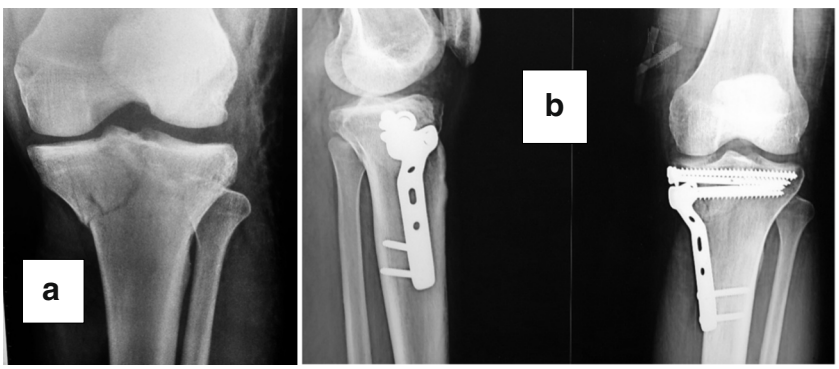

Fig. 3 A 29-year-old male patient after motorbike accident with closed left tibial plateau fracture type AO 41-B1 (**a**). He did not receive HA injections but regained a pain-free range of motion of 5° extension to 120° after ORIF. X-ray at 24-month follow-up (**b**)

Table 2 Time to full weight-bearing (FWB)

Method		Minimum	Maximum	Mean	Std. deviation
Injection (group A)	FWB	12 weeks	18 weeks	14.3158	1.94515
Non-injection (group B)	FWB	12 weeks	18 weeks	14.9474	1.80966

arthroscopic lavage was sufficient to clear the infection. In group B, one patient responded well to matched antibiotic therapy, two patients needed VAC therapy, and one patient was treated by arthroscopic lavage. However, we could not establish a relationship between IA HA and infection. ORIF-related complication occurred in five (25%) group A and in five (25%) group B patients and were statistically insignificant (p value 0.710) (Table 7).

Discussion

Preventing arthritic change in a joint with an intra-articular fracture remains challenging, especially in weight-bearing joints. HA has shown some effectiveness in relieving joint pain and improving function in chronic osteoarthritis. However, controversy still exists about its potential use in a joint with an intra-articular fracture and about whether this effect is dependent on its molecular weight [8].

Prevention of PTOA progression at an early stage becomes an important strategy, particularly in young patients. Recent studies revealed that activated fibroblast-like synoviocytes (FLS) may release cytokines and enzymes such as interleukin (IL)-1β, matrix metalloproteinases (MMPs), and tumor necrosis factor (TNF)-α, which further destroy the surrounding cartilage [1, 18].

High molecular weight HA is more effective in downregulating pro-inflammatory cytokines such as interleukin-1β and tumor necrosis factor-α, whereas HA with a low molecular weight has greater efficacy in upregulating anti-catabolic enzymes, such as tissue inhibitor of metalloproteinase-1 and tissue inhibitor of metalloproteinase-2, and in suppressing the catabolic enzyme, matrix metalloproteinase-3, which is thought to be more chondroprotective [8].

In this study, only Hyalgan® (Fidia Pharma USA Inc., Parsippany, NJ, USA), a high molecular weight HA (500,000–730,000 Da) was applied, and therefore the possible beneficial effect of low molecular weight HA was not tested in this study.

To determine positive predictors of intra-articular HA injections, Bowman et al. found in their study involving 102 patients that patients with mild-to-moderate OA, positive responders to the first injection, and patients elder than 60 years would benefit more from a subsequent injection series [19].

Campos and colleagues compared the use of triamcinolone and hylan GF 20 and hylan GF 20 + triamcinolone in severe knee OA and concluded that viscosupplementation with hylan had beneficial effects within 3 months of injection. However, an inferiority of triamcinolone could not be verified [20].

Westrich et al. reported the result of 46 patients with early OA and a symptomatic meniscal tear who underwent knee arthroscopy. They were randomly assigned to receive either three IA HA injections or no IA HA. Patients were evaluated at three and six months. Study results showed that patients treated with IA HA had significantly less pain (according to visual analog scale) at three month follow-up and more flexion at six month follow-up. In addition, patients who received IA HA were more likely to have no tenderness, pain on motion, or crepitus when compared with control patients at the three and six month follow-ups [21]. Comparable results can be reported from this study as the KOOS pain score in the 20 patients was significantly better than in the control group. Indeed, in the underlying study, the difference of the mean KOOS pain score was 7.93 ($p = 0.01$) which just falls below the KOOS authors' approved value of 8–10 [22].

Table 3 KOOS with its 5 dimensions

Method		Minimum	Maximum	Mean	Std. deviation	p value
Injection (group A)	KOOS symptoms	64.29	78.57	70.6784	4.69695	0.09
Non-injection (group B)	KOOS symptoms	64.29	82.14	75.3967	5.72889	
Injection (group A)	KOOS pain	72.22	88.89	79.6842	3.82076	0.01
Non-injection (group B)	KOOS pain	63.89	77.78	71.7583	4.88255	
Injection (group A)	KOOS function	52.94	82.35	71.6700	8.73900	0.321
Non-injection (group B)	KOOS function	52.94	77.94	69.5056	5.68741	
Injection (group A)	KOOS sport	50.00	85.00	73.9474	9.51300	0.747
Non-injection (group B)	KOOS sport	65.00	85.00	73.0556	6.88965	
Injection (group A)	KOOS QOL	56.25	87.50	74.3116	10.17121	0.335
Non-injection (group B)	KOOS QOL	62.50	87.50	77.0678	6.45284	

Table 4 Comparison of IKDC with and without injection

Method		Minimum	Maximum	Mean	Std. deviation	*p* value
Injection (group A)	IKDC	62.10	80.50	72.43	5.347	0.718
non-injection (group B)	IKDC	55.20	81.60	71.70	6.80	

However, in a recent study by Lyman et al., patient-reported outcome measures (PROMs) in THA and TKA procedures as KOOS and HOOS (Hip Disability and Osteoarthritis Outcome Score) and KOOS (JR) and HOOS (JR) (JR (joint replacement)) were evaluated regarding their validity for the minimal clinically important difference (MCID) calculated using distribution and anchor-based methods by determining whether they surpass the minimal detectable change (MDC). The authors found that depending on the confidence interval selected for the MDC, values reached from seven to 16 for the HOOS and KOOS domains and the JRs. The MCIDs stretched from 6 to 9 for the distribution-based approach and seven to 36 for the anchor-based approach, concluding that MDC and MCID differ greatly based on assumptions and methods used [23].

In a pilot study, Clarke et al. addressed the therapeutic and adverse effects of intra-articular IA HA in 43 patients with evidence of isolated patellofemoral osteoarthritis of the knee. From four weeks after injection to 26 weeks, they reported a significant improvement of patient and clinician global rating and pain on stair climbing. Adverse knee events occurred in 18.6% of patients within 48 hours, but only two failed to complete the course of injections because of adverse knee events [24].

The underlying study included in group A two (10%) patients with infection, two (10%) with limited knee range of motion, and three (15%) with fracture-related painful hardware. In group B, there were four (20%) patients with infection, two (10%) with limited knee range of motion, two (10%) with fracture-related painful hardware, and one patient with DVT in the fractured limb. We could not verify any relationship between IA HA application and infection rate in this small number of patients.

Huang et al. assessed 120 patients with isolated ACL injury who had received patellar tendon autograft reconstruction and were randomly assigned to 4 groups (groups 1–4, 30 patients each). All patients received 16 weeks of regular rehabilitation and IA HA (groups 1–3) or saline injections (group 4) weekly for three weeks. Additionally, patients in group 1 received HA starting at four weeks after surgery, patients in group 2 received HA at eight weeks, and patients in group 3 received HA at 12 weeks post-operatively. Results from this trial showed that patients in groups 2 and 3 showed more improvement in ambulation speed and muscle peak torque after the rehabilitation program and at follow-up than those in group 4. The best results at one year after treatment occurred in the group that received HA at eight weeks after surgery (group 2) [25]. Conversely, group A patients received the initial IA HA injection immediately after ORIF, and delayed application of IA HA was not done in this study.

In 2007 Hempfling showed the short- and long-term effects of combining IA HA with knee arthroscopy in a total of 80 patients with persistent knee pain. Forty patients underwent arthroscopic knee joint lavage, in some cases combined with careful cartilage debridement, while another 40 patients underwent the same procedure which, after final joint lavage, was immediately followed by a single administration of HA. Assessments carried out three months after treatment indicated that restricted ability to walk 100 metres, pain on walking, night pain, and clinical global impression were equal or improved in patients who received HA in addition to arthroscopy, whereas these deteriorated in those managed with arthroscopy alone. Additional follow-up at one year with the same measurements indicated that these between-group differences persisted up to this time point [26].

These results support the efficacy of IA HA in patients with early OA or ACL injury. However, it must be noted that the abovementioned number of studies (4) and patients ($n = 289$) is low and that one of the trials did not include a control group. Larger-scale randomized controlled trials are needed to further evaluate the efficacy of IA HA in early OA before it can be recommended for use in this setting. The major deficiency of this study is the absence of a "true" placebo group which was rejected in the local ethic board proceedings for fear of infection. Other clear shortcomings of this study include the small patient number, the select use of high molecular weight HA, the short follow-up period (total average 23 months), the unblinded study design, and the inability to determine an associated increased risk of knee infection. Another debatable issue is the application of the first IA HA injection in the presence of an extra-articular non-suction drain in the setting of an arthrotomy approach.

Nevertheless, it is possible that patients who begin IA HA treatment at a younger age may have a greater total number of

Table 5 Time to full radiological union

Method		Minimum	Maximum	Mean	Std. deviation	*p* value
Injection (group A)	Time to full union	12 weeks	20 weeks	14.63	2.36	0.998
Non-injection (group B)	Time to full union	12 weeks	20 weeks	14.72	2.24	

Table 6 Multivariate testing showing the significant effect of HA injections

Multivariate tests[a]

Effect		Value	*F*	Hypothesis df	Error df	Sig.	Partial eta squared	Non-cent. parameter	Observed power[c]
Intercept	Pillai's trace	0.999	2689.961[b]	9.000	23.000	0.000	0.999	24,209.650	1.000
	Wilks' lambda	0.001	2689.961[b]	9.000	23.000	0.000	0.999	24,209.650	1.000
	Hotelling's trace	1052.593	2689.961[b]	9.000	23.000	0.000	0.999	24,209.650	1.000
	Roy's largest root	1052.593	2689.961[b]	9.000	23.000	0.000	0.999	24,209.650	1.000
HA injection	Pillai's trace	0.614	4.074[b]	9.000	23.000	0.003	0.614	36.662	0.968
	Wilks' lambda	0.386	4.074[b]	9.000	23.000	0.003	0.614	36.662	0.968
	Hotelling's trace	1.594	4.074[b]	9.000	23.000	0.003	0.614	36.662	0.968
	Roy's largest root	1.594	4.074[b]	9.000	23.000	0.003	0.614	36.662	0.968
Sex	Pillai's trace	0.257	0.882[b]	9.000	23.000	0.555	0.257	7.942	0.324
	Wilks' lambda	0.743	0.882[b]	9.000	23.000	0.555	0.257	7.942	0.324
	Hotelling's trace	0.345	0.882[b]	9.000	23.000	0.555	0.257	7.942	0.324
	Roy's largest root	0.345	0.882[b]	9.000	23.000	0.555	0.257	7.942	0.324
Fracture site	Pillai's trace	0.326	1.235[b]	9.000	23.000	0.322	0.326	11.119	0.455
	Wilks' lambda	0.674	1.235[b]	9.000	23.000	0.322	0.326	11.119	0.455
	Hotelling's trace	0.483	1.235[b]	9.000	23.000	0.322	0.326	11.119	0.455
	Roy's largest root	0.483	1.235[b]	9.000	23.000	0.322	0.326	11.119	0.455
HA injection × sex	Pillai's trace	0.414	1.803[b]	9.000	23.000	0.122	0.414	16.229	0.645
	Wilks' lambda	0.586	1.803[b]	9.000	23.000	0.122	0.414	16.229	0.645
	Hotelling's trace	0.706	1.803[b]	9.000	23.000	0.122	0.414	16.229	0.645
	Roy's largest root	0.706	1.803[b]	9.000	23.000	0.122	0.414	16.229	0.645
HA injection × fracture site	Pillai's trace	0.341	1.323[b]	9.000	23.000	0.279	0.341	11.903	0.486
	Wilks' lambda	0.659	1.323[b]	9.000	23.000	0.279	0.341	11.903	0.486
	Hotelling's trace	0.518	1.323[b]	9.000	23.000	0.279	0.341	11.903	0.486
	Roy's largest root	0.518	1.323[b]	9.000	23.000	0.279	0.341	11.903	0.486
Sex × fracture site	Pillai's trace	0.000	.[b]	0.000	0.000	.	.	.	.
	Wilks' lambda	1.000	.[b]	0.000	27.000	.	.	.	.
	Hotelling's trace	0.000	.[b]	0.000	2.000	.	.	.	.
	Roy's largest root	0.000	0.000[b]	9.000	22.000	1.000	0.000	0.000	0.050
HA injection × sex × fracture site	Pillai's trace	0.000	.[b]	0.000	0.000	.	.	.	.
	Wilks' lambda	1.000	.[b]	0.000	27.000	.	.	.	.
	Hotelling's trace	0.000	.[b]	0.000	2.000	.	.	.	.
	Roy's largest root	0.000	0.000[b]	9.000	22.000	1.000	0.000	0.000	0.050

[a] Design, intercept + HA injection + sex + fracture site + HA injection × sex + HA injection × fracture site + sex × fracture site + HA injection × sex × fracture site

[b] Exact statistic

[c] Computed using alpha =

injections over their lifetime than older patients. Thus, additional long-term safety data for IA HA could also support a recommendation for use in early OA.

Recently, other biologicals have been extensively investigated.

After conducting arthroscopic debridement in 52 patients with early knee OA, Schiavone Panni et al. reported improved clinical and functional improvement after intra-articular injection of autologous adipose-derived stem cells (aASCs) at an average follow-up of 15.3 months, particularly in patients with higher baseline VAS scores [27].

Similarly, Hong et al. used autologous adipose-derived stromal vascular fractions (SVF) in 16 patients with bilateral knee OA in one knee. The other symptomatic knee was injected with HA, and the authors report effective pain relief and improved function in SVF knees [28]. Nevertheless, this study was criticized for its small number and for methodological shortcomings [29].

Table 7 Complications

Method		Frequency
Injection group A	Infection	2 (10%)
	Limitation of movement	2 (10%)
	Painful hardware	3 (15%)
	No complications	13 (65%)
	Total	$n = 20$ (100%)
Non-injection group B	Infection	4 (20%)
	Limitation of movement	2 (10%)
	Painful hardware	2 (10%)
	DVT	1 (5%)
	No complications	11 (55%)
	Total	$n = 20$ (100%)

Hernigou et al. used autologous subchondral stem injections in corticosteroid-induced bilateral osteonecrosis of the knee in 30 young patients in one knee and total knee arthroplasty in the other knee and reported at an average follow-up of 12 years results favouring the use of subchondral bone marrow injections [30].

A systemic review by Krstičević et al. regarding the efficacy and safety of proliferative injection therapy (prolotherapy) in the treatment of OA revealed limited proof for a positive effect as the seven included random controlled trials comprised only a limited number of patients and displayed methodological flaws [31].

Centeno and colleagues examined the adverse effects of autologous stem cell therapy in several orthopaedic conditions in a large multicenter study including 2372 patients. The most common adverse effects were post-procedural pain encountered in 93 patients (3.9%) and progressive joint degeneration pain in 90 patients (3.8%). Bone marrow concentrates (BMC) had the least adverse effects when compared with BMC enhanced with fat or cultured cells [32].

Conclusion

These study results show that patients treated with intra-articular hyaluronic acid injection after fixation have significantly less pain (KOOS). No significant difference was found between both groups in symptoms, complications, functional outcome, or quality of life.

These preliminary results support a direct role for hyaluronic acid in the acute phase of the inflammatory process that follows articular injury and provides initial evidence of efficacy for IA HA. This study serves as a stimulus for larger prospective multicentric studies so that clear recommendations can be provided.

Compliance with ethical standards

This work was conducted at Cairo University Hospitals in accordance with the ethical standards of the Helsinki Declaration. All participating patients signed an informed consent regarding the procedure, possible complications, and alternative treatment modalities.

Conflict of interest The authors declare that there is no conflict of interest.

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