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Journal of Clinical Trials

Research Article

Effects of Hyaluronic Acid-Sorbitol Formulation in Patients Undergoing Knee Arthroscopy: A Randomized Controlled Single-Blind Clinical Trial

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ABSTRACT

Background: Although there is no best irrigation solution for knee arthroscopy, many studies show that the most commonly irrigation fluids are toxic for the articular chondrocytes, suppressing their metabolism and function. The purpose of this study is to evaluate the clinical outcome of patients injected with 6 ml of hyaluronic acid (2%) and sorbitol (4%) formulation (Synolis VA) after knee arthroscopy and compare pain and functionality outcomes with patients who did not receive Synolis VA in the post-operative period.

Materials and Methods: 60 patients were randomly divided using a computer-produced causal number generator algorithm into 2 groups. At the end of the procedure 30 patients received an intra-articular 6ml injection of Synolis VA the remaining 30 patients did not receive any treatment. Inclusion criteria: age 18 to 60 years, meniscectomy or debridement and lavage for cartilage lesions (non-bleeding knee arthroscopy), body mass index (<30). Patients with joint-line misalignment, ligamentous lesions, synovial membrane pathology or inflammatory joint disease were excluded from the study. Patients were reviewed at several follow-up points and monitored using outcomes such as the IKDC subjective knee evaluation score, pain variation (using VAS and WOMAC pain sub-score) and variation of stiffness (using WOMAC stiffness sub-score). Patients were also asked to fill in a self-assessment questionnaire on a weekly basis. The statistical analysis was performed with IBM SPSS Statistics for Windows, Version 28.0.

Results: Patients injected with Synolis VA showed better clinical outcomes in the first 4 weeks' post-intervention compared to patients that were not injected with the product; these patients had higher IKDC Subjective Knee Evaluation scores, as well as lower subjective pain scores and reduced stiffness.

Conclusion: Based on our results, post-operative injection with Synolis VA in patients undergoing non-bleeding knee arthroscopy for degenerative and traumatic pathology, effectively reduces pain and improves mobility in the short-term post-operative phase.

Keywords: Knee osteoarthritis; Synolis VA; Patient; Pain; Clinical trial

ABBREVIATIONS

Synolis VA: 6 ml of Hyaluronic acid (2%) and Sorbitol (4%) formulation; OA: Osteoarthritis; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; IKDC: International Knee Documentation Committee; VAS: Visual Analogue Scale; BMI: Body Mass Index; HA: Hyaluronic Acid

INTRODUCTION

Knee osteoarthritis (OA), is the most common multifactorial joint disease of adults worldwide, characterized by cartilage matrix degradation, chronic pain physical disabilities and reduction of quality of life [1,2]. From a histopathological point of view, there is an imbalance in cartilage homeostasis between

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Received: 21-Feb-2025, Manuscript No. JCTR-25-37036; **Editor assigned:** 24-Feb-2025, PreQC No. JCTR-25-37036 (PQ); **Reviewed:** 12-Mar-2024, QC No. JCTR-25-37036; **Revised:** 20-Mar-2025, Manuscript No. JCTR-25-37036 (R); **Published:** 28-Mar-2025, DOI: 10.35248/2167-0870.25.S32.004

Citation: Giusti S, Paola BD, Fenu ED, Caria C, Adriani E (2025). Effects of Hyaluronic Acid-Sorbitol Formulation in Patients Undergoing Knee Arthroscopy: A Randomized Controlled Single-Blind Clinical Trial. J Clin Trials. S32:004.

the destruction and self-repair mechanisms: an increased expression of pro-inflammatory cytokines (IL-1, TNF alpha), of metalloproteinase of the matrix, of prostaglandins and nitric oxides; a reduced synthesis of growth factors, collagen, proteoglycans and anti-inflammatory cytokines (IL-4 and IL-10) [3.4].

Surgery is indicated in patients who are not responsive to conservative treatment and who therefore continue to show limitations in their daily activities with variations in their lifestyle. The most invasive surgical treatments include interventions such as corrective osteotomies or joint arthroplasty. However, in those cases where the arthroscopic disease has not yet evidenced major anatomo-pathological alterations, a solution may be given by Arthroscopic Debridement (AD), possibly associated with Hyaluronic Acid (HA) infiltra-tions or, more recently, with mesenchymal stem-cell-rich adipose tissue [5]. Whilst the AD aims to eliminate intra-articular loose bodies, unstable meniscal injuries, and / or cartilage flaps, the purpose of HA infiltrations is to restore joint balance.

Knee arthroscopy complications are relatively low (0.56/1.68%), however some patients can still experience pain, swelling or stiffness during the post-operative period [6-8]. In addition to being caused by surgical stress, these issues are also likely to depend on the negative influence of the irrigation fluid (saline) used during arthroscopy, which has been shown to have an adverse effect, although temporary, on the metabolism of the articular cartilage promoting the release of catabolic molecules and pro-inflammatory factors [9-11]. The rationale of administering HA infiltrations is directly connected to reducing cellular stress, reducing pain, facilitate shock absorption because of its viscoelastic proper-ties, retain fluids in the joint cavity during movement thanks to its macromollar size, re-duce deterioration and finally, by facilitating the synthesis of aggregates in the articular tissues, modulate inflammatory activities [12].

Based on the literature regarding the biomechanical and biological actions of Hyaluronic Acid (HA), it is clear how it could play a crucial role in speeding up the recovery process; encouraging results have already been documented.

The purpose of this study is to evaluate the clinical outcome of the effects of injecting a combination of hyaluronic acid (2%) +sorbitol (4%) (Synolis VA®) with high molecular weight in patients undergoing knee arthroscopy, with the hypothesis that this will improve pain and functionality outcomes, especially in the initial post-operative phase.

MATERIALS AND METHODS

The study was a prospective, randomized-controlled clinical trial. The study was carried out in our facility over a period of 12 months. Ethical approval was obtained by the local ethical committees (IRB 21.19 TS). The study was conducted according to the Helsinki declaration.

Randomization was obtained using a computer-produced causal number generator algorithm so as to form 2 groups:

Study group (A): received a single injection consisting of a combination of hyaluronic acid (MW 2MDa, 40 mg/2 ml) and sorbitol (80 mg/2 ml) (Synolis VA®, Aptissen, Switzer-land);

Control group (B): did not receive the injection after the procedure.

All patients were blinded and did not know whether they had received the injection or not.

Inclusion criteria

Patients aged between 18 and 60, BMI less than 30, who required knee arthroscopy for mechanical symptoms due to meniscal and/or cartilage lesions (younger patients) or signs of grade 1 or 2 osteoarthritis according to Kellgren-Lawrence.

Patients were excluded if any of the following applied: not within the age group limit, BMI> 30, ligamentous lesions, bone diseases, synovial membrane diseases, rheumatoid arthritis or other inflammatory diseases, pregnancy.

All patients underwent a clinical-instrumental screening (conventional X-rays and Magnetic Resonance Imaging (MRI)) prior to the operation and on the day of the procedure they signed an informed consent form to receive the treatment and participate in the study. The same senior surgeon performed all arthroscopic procedures in the same centre under spinal anesthesia, through standard anteromedial and anterolateral portals. In all cases, an arthroscopic pump and Tourniquet (250 mmHg only during the surgical phase, average time 17 minutes) were used. The procedures included treatment of any meniscal lesions, debridement of joint cartilage and removal of any meniscal flaps. No micro-fractures were performed. At the end

Table 1: Patient demographics.

	Arthroscopy + < Synolis (n=30	Arthroscopy (n=30
Age (years)	42 (23-58)	41 (19-59)
Patient sex (male)	22 (30)	21 (30)
Body Mass Index (Kg/m^2)	26.2 (3.3)	27.7 (2.2)

Note: Values are presented as mean (standard deviation) or count (proportion).

of the arthroscopic procedure, the injection was performed *via* the anterolateral portal under dry-arthroscopic monitoring to be certain of the intra-articular insertion of the HA.

Both groups underwent an accurate drainage of arthroscopic irrigation fluids, suturing of the arthroscopic portals and compression bandaging. In no case were articular drains placed. The surgeon was not informed which group the patient belonged to until the end of the procedure when he injected the Synolis VA in the selected cases. The senior surgeon did not participate in the subsequent collection of data and patient evaluation. All patients received a short acting spinal anesthetic+ local femoral block administered by one of two senior anesthetists. No braces were placed in the post-operative period. The re-habilitation protocol was standard for all patients. This included an initial 2-week early phase focusing on "early functional" rehabilitation and immediate weight bearing as tolerated. Following the first 2 weeks, patients underwent further 2 weeks of "progressive functional" rehabilitation, focusing on strength, proprioceptive and neuro-motor control of all muscle groups.

All patients were evaluated before the operation (D0), at 1 week (W1), 1 month (W4) and 3 months (W12) post-operative. Further patient clinical parameters were recorded from week 3 (W3) to W12, *via* questionnaires to be filled out at home with the aim of evaluating pain and functional recovery every week from the third week after the procedure up to the final week. The self-evaluation questionnaires included: the subjective International Knee Documentation Committee (IKDC) score, the Western Ontario and the McMaster University (WOMAC) stiffness sub-score and the WOMAC Pain sub-scales.

RESULTS

A total of 60 patients were enrolled starting March 2024 for a duration of nearly 3 months.

- Group A (30 patients): Mean age 42 years (range 23-58); mean BMI 25.5 (range 20.1-29.6), 27% women and 73% men.
- Group B (30 patients): Mean age 41 years (range 19-59); mean BMI 23.4 (range 19.8-27.3), 30% women and 70% men.

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 28.0 (IBM Corp., Armonk, N.Y., USA). Analysis of variance (ANOVA) was performed according to compare outcome between groups. Differences were considered significant at the $p < 0.05$ level.

At D0 the majority patients had pain and functional limitation, expressed as stiffness, from moderate to severe (Tables 2,3,4). At W1 and W4 we observed an improvement in IKDC scores for both groups, however the improvement was greater in the intervention Group A. (Table 5). Similar results were also seen when comparing WOMAC Pain and Stiffness scores where Group A patients had greater reduction in both pain and stiffness (Tables 6, 7). Furthermore, Group A patients reported better performance in activities of daily living 1 month after the procedure and less interference with sports participation during the first post-operative recovery phase. All of these findings were statistically significant ($P<0.05$). However, at the final W12 control we did not notice any statistically significant difference between the two groups in any of the parameters.

We also considered the administration of any type of analgesic medication in the post-operative period. All of our patients followed our standard protocol which includes 1g of oral Paracetamol administered 3 times per day at 8:00 AM, 14:00 PM and 20:00 PM for 5 days + 10mg of oral Ketoralac to be taken in case of pain a maximum of 3 times per day for 5 days. All patients had proton-pump inhibitor prophylaxis. We highlighted how in Group A only 5 patients (5%) took Ketoralac in the first 5 days' post-op compared to 24 patients in Group B (80%) - these findings were statistically significant.

Table 2: Pre-operative subjective IKDC score in patients who received the intervention (Group A) *vs.* patients who did not receive the intervention (Group B).

IKDC scores				
	<20%	20-35%	35-50%	>50%
Group A	5	10	12	3
Group B	5	4	18	3

Table 3: Pre-operative subjective WOMAC stiffness score in patients who received the intervention (Group A) *vs.* patients who did not receive the intervention (Group B).

WOMAC stiffness scores			
	<10	10-15	>15
Group A	7	18	5
Group B	9	17	4

Table 4: Pre-operative subjective WOMAC pain score in patients who received the intervention (Group A) *vs.* patients who did not receive the intervention (Group B).

WOMAC pain scores				
	<20	20-30	30-40	>40
Group A	1	10	16	3
Group B	0	14	113	3

Table 5: Mean subjective IKDC score progression in patients who received the intervention (Group A) *vs.* patients who did not receive the intervention (Group B).

Subjective IKDC score means at various intervals (days post-operative)				
Days	0	7	30	90
Group A (%)	34	69	87	96
Group B (%)	38	59	76	93

Table 6: Mean subjective WOMAC stifness score progression in patients who received the intervention (Group A) *vs.* patients who did not receive the intervention (Group B).

Subjective WOMAC stiffness score means at various intervals (days post-operative)				
Days	0	7	30	90
Group A	11.8	5.7	2.9	2.3
Group B	11.2	7.7	3.8	2.8

Table 7: Mean subjective WOMAC pain score progression in patients who received the intervention (Group A) *vs.* patients who did not receive the intervention (Group B).

Subjective WOMAC pain score means at various intervals (days post-operative)				
Days	0	7	30	90
Group A	31.1	14.8	7.4	4.9
Group B	30.4	20.0	10.9	5.1

DISCUSSION

Knee arthroscopy is an option for treating cartilage, meniscal lesions, and early OA pictures as it may result in symptomatic relief and functionality improvement. It is also a procedure with minimum morbidity, which allows for both excellent diagnostics and treatment of multiple conditions [6].

Recent studies confirm that arthroscopic surgery may be an appropriate surgical treatment in patients with preoperative

mechanical symptoms caused by free bodies, chondral flaps, and meniscal disorders [13]. In fact, it has been shown that more than 90% of patients with symptomatic knee OA will have magnetic resonance imaging indicating meniscal pathology [14].

For these reasons, arthroscopy can be a viable option to perform articular lavage with reduction of the biochemical agents of the inflammation, partial meniscectomy for unstable meniscus tears, partial synovectomy, removal of free bodies, and chondral cartilage shaving, resulting in symptomatic relief and functional improvement, reducing the need for major knee surgery [15,16]. However, in some cases, there may be complications during the post-operative phase of an arthroscopic procedure, such as persistence of swelling, pain, and sometimes reduction of the articular range. It is clear that these adverse events largely depend on surgical stress, but several studies have shown that the irrigation fluid can also be a contributing factor [9,10,11,17].

During arthroscopy, irrigation with NaCl solution results in a dilution of the synovial fluid with a decrease in Hyaluronic Acid (HA) concentrations and therefore a decrease in its physical characteristics and protective functions, which can lead to a greater cartilage vulnerability. According to various studies, this greater vulnerability to mechanical stresses of the cartilage may depend on the irrigation with NaCl which inhibits the metabolism of the chondrocytes during the first 7 days' post-procedure. A serious reduction in the number of cells is in fact observed in an isotonic sodium chloride solution. The density reduction observed in these cells is not simply the result of the loss of adherence between them as is noted with a low pH, but also a reduced cellular vitality [10,18]. Similar effects are not however observed with Ringer's lactate solutions which are able to maintain the cellular integrity and morphology and are therefore considered to be the gold-standard solution for arthroscopy irrigation [19].

Matsusue and Thomson reported a positive result in 87% of patients undergoing arthroscopic meniscectomy with OA grade I or II [20]. Bin et al., observed that 90% of patients undergoing arthroscopic meniscectomy despite a 4th level chondropathy on the medial femoral condyle according to Outerbridge, had better subjective results on the VAS and Lysholm scoring scales [21,22]. Therefore, it can be argued that arthroscopy constitutes a good therapeutic alternative for subjects without severe radiographic signs of OA or ones for whom the mechanical problem is dominant or arthroplasty is not recommended. However, the duration of the symptomatic benefits is extremely variable, and the procedure is often characterized by persistence of those same symptoms that led to the surgery (pain, functional limitation, reduction of patient comfort). This adverse event is often followed by a slower functional recovery.

Therefore, an increasing number of studies considers the possibility of terminating the surgical procedure with the use of an adjuvant capable of quickly restoring the correct equilibrium of the joint environment. In particular, the focus turned towards HA, which, amongst other things, shows alterations of its properties in the case of OA (reduction in molecular weight and concentration) which lead to a lower degree of viscosity of the synovial fluid [23,24].

Marshall et al., were amongst the first to report the intra-articular use of HA (hylan G-F 20) in patients with persistent symptoms after their AD [25]. This study, published in 1996, showed that most patients had a "severe" or "marked" OA, but in 68% of cases no subsequent knee arthroplasty was required, and they were assessed as "recovered".

In 2002 Chen et al., administered HA to 77 patients with OA after knee arthroscopy and compared these with the control group for which only the surgical procedure had been performed [26]. The HA group had better results in terms of muscle strength and VAS, concluding that HA was an important element. In 2007, Hempfling reported the results of a randomised, controlled, double-blind trial with 80 patients undergoing arthroscopic knee wash [27]. 40 patients were also administered 10 ml of hyaluronic acid. Both groups had positive

Table 8: Summary of the most relevant biochemical effects of Hyaluronic Acid.

Summary of the most relevant biochemical effects of Hyaluronic Acid
Cell signaling
Inflammatory response
Mitochondrial function
Extracellular matrix organization
Antioxidation
Viscosupplementation
Wound healing
Tumour progression
Protease inhibition

effects 3 months after the surgical procedure, but the effect lasted for 1 year for patients who received HA.

The rationale of the HA use derives from the fact that during the AD procedure, joint irrigation removes the synovial fluid and the HA layer above the cartilage with a loss of proteoglycans and this determines adverse effects on the metabolism and on the structure of the cartilage itself [28,29]. Jansen et al., in a recent study showed that hyaluronic acid has a potential role in preventing the death of articular cartilage cells in the presence of joint lesions [30]. Therefore, the main role of HA is to maintain the structural and functional characteristics of the extracellular matrix of the cartilage and of the biological fluids. HA improves the properties of synovial fluid after arthroscopy, allowing it to regain its physical properties, it acts as a lubricant and joint dampener, it reduces the risk of cell damage or of its development by diminishing any mechanical stress on the joint surface. This, together with its ability to "inhibit" nociceptors of the joint capsule, results in pain reduction, moreover, when HA is introduced into the joint, it contributes to "remove" the saline wash solution, preventing its harmful effects on the cartilage metabolism [31,32].

In another trial, knees with cartilage lesions were irrigated with NaCl while another group was administered HA; 7 days later an improvement was seen in chondrocyte metabolism in patients who received HA compared with the group without HA [10,17].

HA also has a protective role against chondrocytes at the edge of the cartilage lesion. In fact, chondrocytes peripheral to cartilage lesions die due to mechanical compressions. Such apoptosis begins about 6h after the trauma and tends to increase as a percentage up to 7 days after the injury [33,34].

In this regard, Diaz-Gallego et al., have shown that intra-articular HA plays a protective role in cartilage by reducing cellular apoptosis when the treatment is started early following mechanical or physiological stress [35].

However, the long-term effect of HA in relation to the effects on cell death and on the chondrocyte metabolism is still unclear. This strengthens the idea that there is a "therapeutic window" in which to use the HA to achieve maximum results.

As evidenced by the literature, our trial also showed how the group receiving HA injections had an improved recovery in their activities of daily living during the first postoperative week and a faster recovery of amateur sports activity one month later compared with the control group. This improved functional aspect is clearly linked to a lower incidence of postoperative pain, which is also confirmed by the reduction in analgesic usage. However, at the 3-month control no differences were observed in the functional results between the two groups, confirming that the use of HA does not affect the final outcome of the surgical procedure, but represents an adjuvant to an easier recovery. In particular, we have chosen Synolis VA because of its elevated concentration of NaHA (20 mg/ml, 2%) which helps to modulate the release of inflammatory agents and contributes to maintain the functional and structural features of the extracellular cartilage matrix; high molecular weight (2.2 MDa), reduces the expression of the pro-apoptotic receptors of the Chondrocytes (CD44) the combination with a high dose of Sorbitol (40mg / ml) which on the one hand protects NaHA from the action of free articular radicals, indirectly promoting articular homeostasis, on the other it lowers the free radical concentration, inhibiting the migration of macrophages in the joint cavity and leading to a direct reduction of the inflammation and pain [36-39]. However, the most likely reason for the initial beneficial effects of HA injections in patients undergoing arthroscopy resided in the capacities of HA to bid tightly to its main receptors, CD44 and RHAMM, overexpression of which has been largely associated with pro-inflammatory responses and tumorigenesis [40,41].

Our study had multiple limitations, including the reduced sample size and the large prevalence of male patients included. However, the study was still carried out with all patients blinded as to whether or not they had received the Synolis VA injection and the disparity of male and females was consistent amongst the two groups. A larger sample size would definitely improve the validity of the study.

CONCLUSION

Based on our results, it may be assumed that the use of HA infiltrations after AD on knees with mild or moderate OA leads to better results in terms of postoperative pain and short-term functionality. Further studies with greater follow-ups and larger patient groups are required to justify the use and cost-effectiveness of these post-routine arthroscopy procedures.

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