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Article

Effects of Hyaluronic Acid-Sorbitol formulation in Patients Undergoing Knee Arthroscopy: Effects on Pain and Articular Recovery

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Abstract: Background: Following non-bleeding arthroscopy, patients that are injected with 6 ml of hyaluronic acid (2%) and sorbitol (4%) formulation (Synolis VA) show better results in terms of pain reduction and improved mobility recovery compared to patients that did not receive the treatment.

Introduction: Although there is no best irrigation solution for the knee arthroscopy, many studies showed that the common irrigation fluids, especially cold ones, 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 Synolis V-A after knee arthroscopy.

Materials and Methods: 60 patients were randomly divided into 2 groups. At the end of the procedure 30 patients received an intra-articular injection of hyaluronic acid (2%) and Sorbitol (4%) solution for a total of 6 ml (2 ml per syringe), the remaining 30 patients did not receive any treatment. Inclusion criteria: age (ranging from 18 to 60 years), meniscectomy or cartilage treatment (non-bleeding knee arthroscopy), body mass index (<30). Patients with joint-line misalignment, ligamentous lesions, bone pathology, synovial membrane pathology, rheumatoid arthritis or inflammatory disease, or pregnancy 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 as well as at each visit in order to follow the clinical evolution of the symptoms. The statistical analysis was performed with IBM SPSS Statistics for Windows, Version 28.0. **Results:** Patients injected with Synolis V-A at the short and intermediate check-points showing better clinical results than the patients that were not injected with the product; these patients had higher IKDC Subjective Knee Evaluation scores, as well as lower point of pain and reduced stiffness. **Conclusions:** Based on our results, the injection with hyaluronic acid (2%)/sorbitol (4%) formulation (Synolis V-A) in patients undergoing non-bleeding arthroscopy for degenerative and traumatic changes to the knee joint effectively reduces pain and improves mobility in the short-term post-operative phase.

Keywords: Knee; Arthroscopy; Hyaluronic Acid; Sorbitol; Pain; Stiffness

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 unbalance in cartilage homeostasis between the destruction and self-repair mechanisms: an increased expression of proinflammatory 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 osteotomy or 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) infiltrations or, more recently, with mesenchymal stem-cell-rich adipose tissue (5): whilst the AD aims at eliminating intra-articular loose bodies, unstable meniscal injuries, and / or cartilage flaps, the purpose of HA infiltrations is to restore joint balance.

It is necessary to evaluate why arthroscopic complications are relatively low (0.56 / 1.68%) (6-8), but patients can still experience pain, swelling or stiffness during the post-operative period. 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, (9-11) 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. The rationale of administering HA infiltrations is directly connected to reducing cellular stress, reducing pain, facilitate shock absorption because of its viscoelastic properties, retain fluids in the joint cavity during movement thanks to its macromolar size, reduce 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), an important role could be assigned to HA among the postoperative management options as a reliever accelerant and for recovery from pain.

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.

Materials and Methods

The study was a prospective, randomised, controlled, single-blind, single surgeon 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.

Randomisation 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, Switzerland);

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

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 subarachnoid anaesthesia, through standard antero-medial and antero-lateral portals. In all cases, an arthroscopic pump and Tourniquet (250 mmHg only during the surgical phase) were used. The procedures included treatment of any meniscal lesions, debridement of joint cartilage with the removal of any flaps. No microfractures were performed. At the end of the arthroscopic procedure, the injection was performed via the antero-

lateral 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, arthroscopic portals were sutured, and no drainage was placed. The surgeon was not informed which group the patient belonged to until the end of the surgery, he then injected the product into the knee and did not participate in the subsequent collection of data and patient evaluation. Physical therapy was the same for both groups. All patients were evaluated before the operation (D0), a few hours after the surgical procedure (D1 - only for the WOMAC index), at 1 week (W1), 1 month (W4) and 3 months (W12) after the surgery. 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 score of the International Knee Documentation Committee (IKDC), 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.
- 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 (Tab 1,2,3). At W1 and W4 we observed an improvement in IKDC scale scores for both groups, however the improvement was greater in the intervention Group A. (Tab 4). Similar results were also seen when comparing WOMAC Pain and Stiffness scores where Group A patients had greater reduction in both pain and stiffness (Tab 5, 6). Furthermore, Group A patients reported a better performance in daily life activities 1 month after the procedure and less interference with sports participation (those who performed pre-operative amateur sports activities) during the first post-operative recovery phase. All of these findings were statistically significant ($P < 0.005$). However, at the final W12 control we did not notice any statistically significant difference between the two groups in any of the parameters.

Table 1. Preoperative Subjective IKDC.

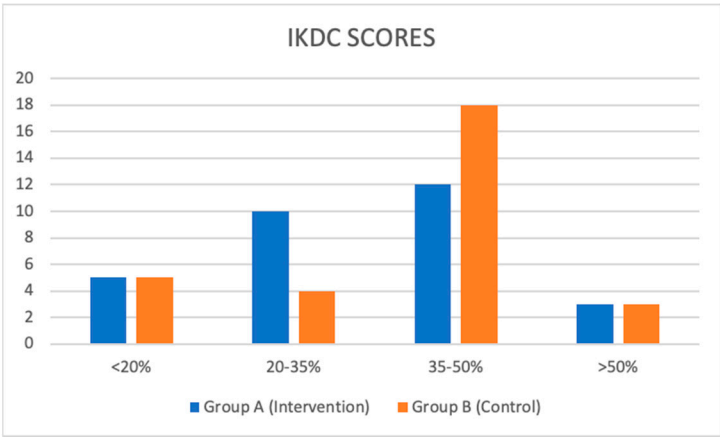


Table 2. WOMAC Preoperative Pain.

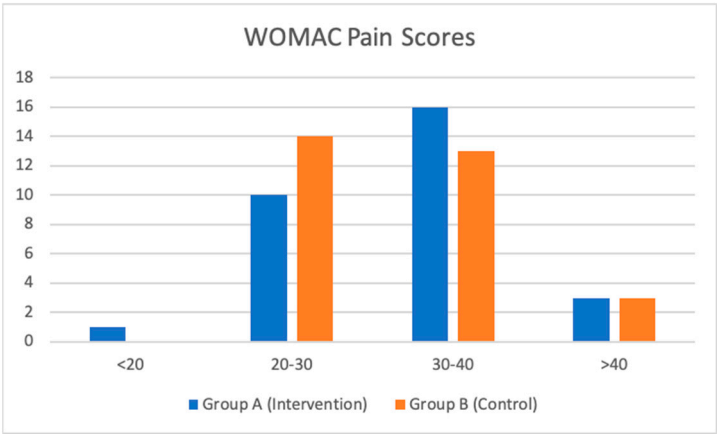


Table 3. WOMAC preoperative stiffness.

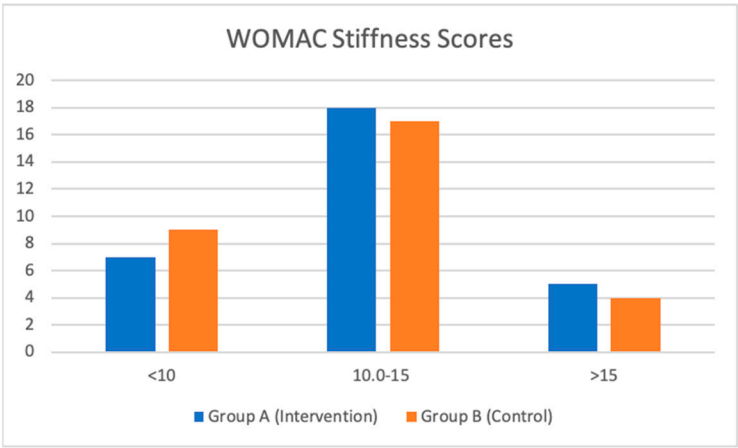


Table 4. IKDC. score improvement at W1 and W4.

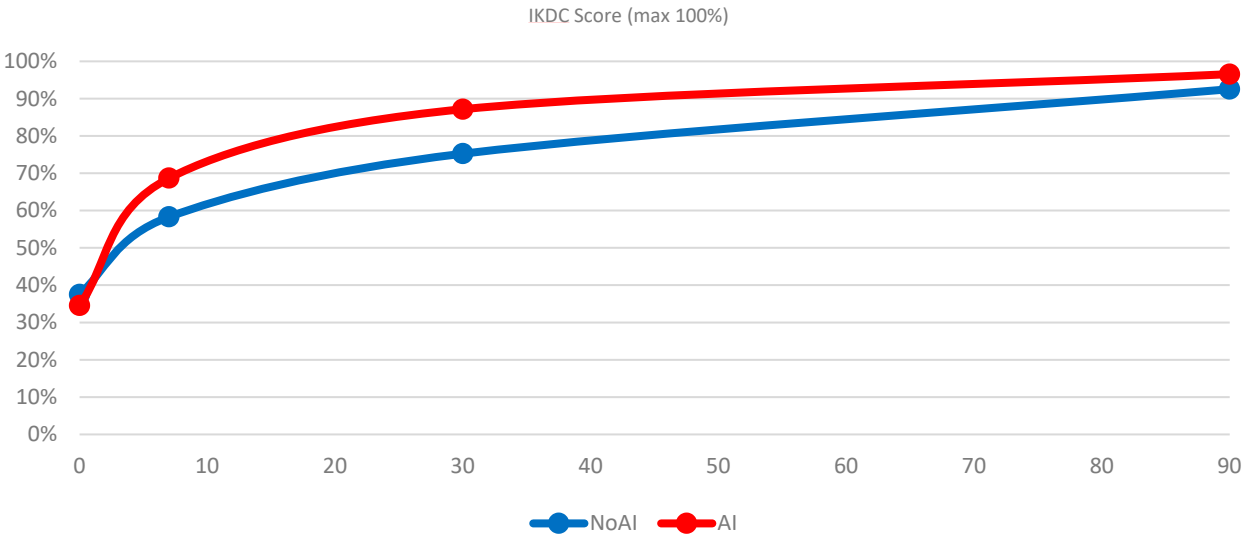


Table 5. WOMAC stiffness. significant improvement at W1 and W4.

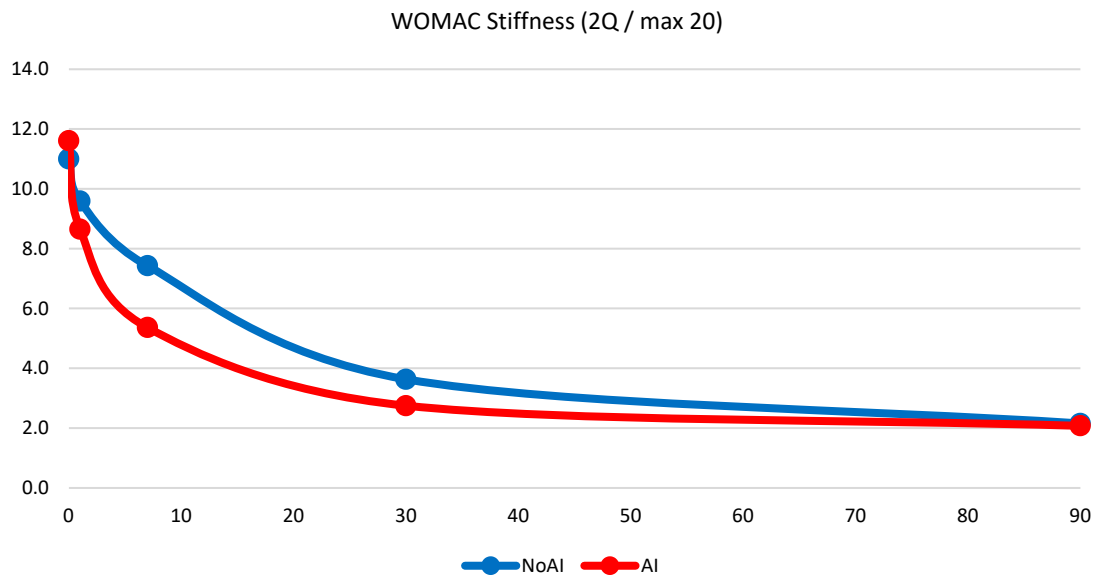
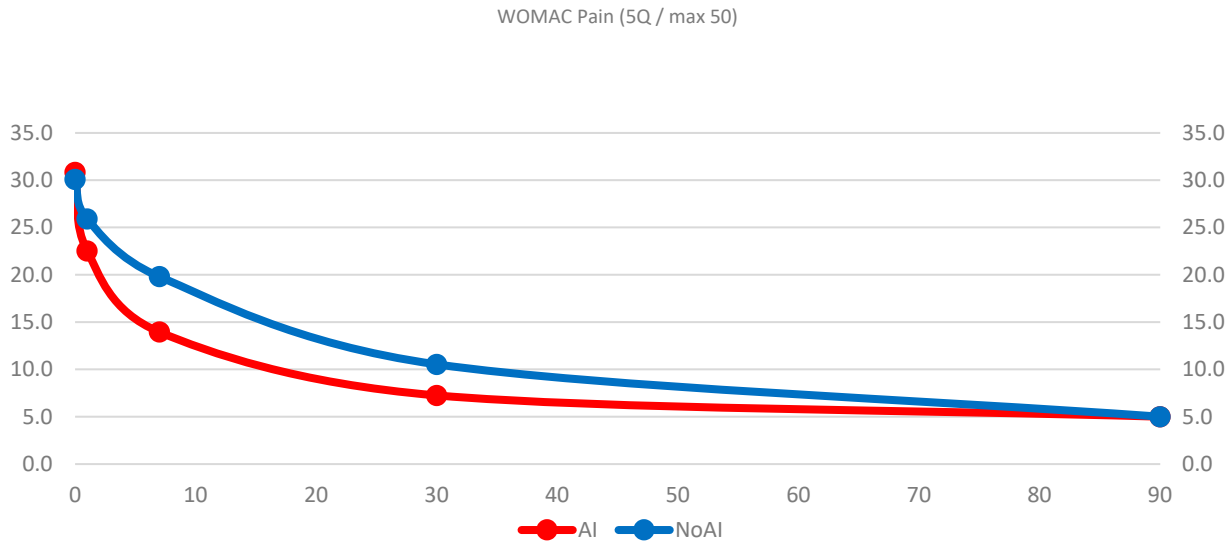
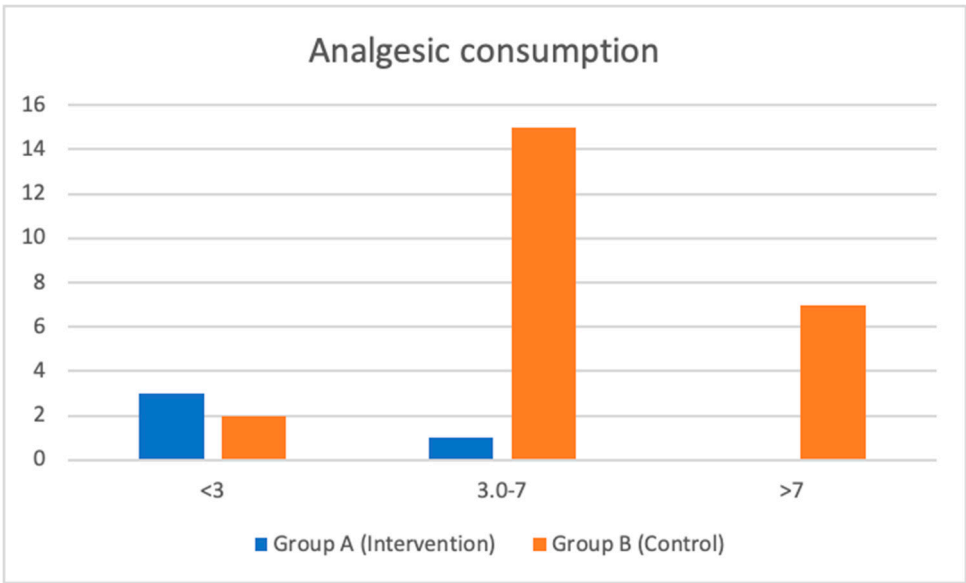


Table 6. WOMAC pain. significant improvement at W1 and W4.



We also considered the administration of any type of analgesic, and we highlighted that in Group A only 5 patients (5%) took anti-inflammatory drugs compared to 24 patients in Group B (80%) (Table 7) – these findings were statistically significant.

Table 7. Intake of analgesic medication in the postoperative period.



Discussion

Knee arthroscopy is an option for treating cartilage, meniscal lesions and early OA pictures as it may result in symptomatic relief, thus improving the function and perception of the subject's health. It is also a procedure with minimum morbidity, which allows documenting the pathological process stage and one which in any case represents a therapeutic procedure (6).

Recent studies confirm that arthroscopic surgery may be an appropriate surgical treatment (13) in patients with preoperative mechanical symptoms caused by free bodies, chondral flaps, and meniscal disorder. In fact, it has been shown that more than 90% of patients with symptomatic knee OA will have magnetic resonance imaging indicating a meniscal pathology (14).

For these reasons, arthroscopy can be a viable option to perform joint wash 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 arthroscopy, 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 in the cells observed 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 (20) reported a positive result in 87% of patients undergoing arthroscopic meniscectomy with OA grade I or II. Bin et al. (21) observed that 90% of patients undergoing arthroscopic meniscectomy despite a 4th level chondropathy on the medial femoral condyle according to Outerbridge (22), had better subjective results on the VAS and Lysholm scoring scales. 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. (25) were amongst the first to report the intra-articular use of HA (hylan G-F 20) in patients with persistent symptoms after their AD. 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. (426) 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. The HA group had better results in terms of muscle strength and VAS, concluding that HA was an important element. In 2007, Hempfling (27) reported the results of a randomised, controlled, double-blind trial with 80 patients undergoing arthroscopic knee wash. 40 patients were also administered 10 ml of hyaluronic acid. Both groups had positive 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. (30) 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. 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 showed in the chondrocyte metabolism 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. And 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 infiltrations had an improved recovery in their daily activity 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 pain-killer 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 V-A because it has a high 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 (36, 37); high molecular weight (2.2 MDa), reduces the expression of the pro-apoptotic receptors of the chondrocytes (CD44) (38); 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 (37, 39).

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 of these post-routine arthroscopy procedures.

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