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RESEARCH ARTICLE

EFFECTIVE USE OF VISCOSUPPLEMENTATION AFTER KNEE ARTHROSCOPY: EXPERIENCE FROM A WORKING GROUP

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Abstract

The aim of this work was to assess the efficacy of viscosupplementation after knee arthroscopy in a series of cases and to propose an adequate dosage regimen. The cases studied corresponded to patients undergoing arthroscopic surgery presenting meniscal injury and/or free bodies and where osteoarthritis could be present. Viscosupplementation started 3 weeks after arthroscopy and one set of patients received one shot of 5 ml of hyaluronic acid and the other set received three injections of 2.5 ml with weekly intervals. Patients were followed at 3 and 6 months. Improvements in pain and function as well as patient satisfaction were assessed and the appearance of adverse events was monitored. The groups studied were homogeneous with no differences in the type of surgery, associated gestures or other procedures performed during the intervention. Considering the patients as a whole, significant improvements were observed at 3 weeks post-arthroscopy (prior to intra-articular treatment) and at 3 and 6 months compared to pre-arthroscopy scores. Pain reductions were of 39.8%, 63.4% and 80.9% respectively and function improvement was of 20.9%, 58.8% and 77.9% respectively. There were no differences between the two groups in any of the parameters analysed. The treatment was rated by the patients as excellent. The group concluded that viscosupplementation in post-arthroscopy achieves significant pain reduction and function improvement; moreover, one shot of hyaluronic acid is a safe and effective option as an adjuvant treatment in arthroscopic surgery, favouring a better recovery with a lower cost for both the patient and the Healthcare System.

Introduction:-

Arthroscopic surgery is a technique that is applied in various joints, the knee being the most common one. Arthroscopy allows particles of different materials present in the joint, such as cartilage fragments and calcium crystals, to be

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eliminated through lavage. It also allows debridement, whereby joint surfaces and osteophytes can be surgically smoothed out.

Knee osteoarthritis (KOA) is a degenerative disease presenting pain, rigidity and reduction of the joint function. It has a multidisciplinary treatment approach that includes non-pharmacological measures, pharmacological treatments and, ultimately, surgery.

The objective of arthroscopic surgery is to reduce synovitis and eliminate mechanical interference with movement of the joint (Kirkley et al, 2008). Although arthroscopic surgery has been used extensively as treatment in KOA, its use is still controversial. Uncontrolled studies in patients with KOA (Felson and Buckwalter, 2002; Mclaren et al, 1991; Ogilvie-Harris and Fitsialos, 1991; Yang and Nisonson, 1995) described the efficacy of arthroscopic surgery in at least 65% of the patients. However, other controlled and randomised trials (Kirkley et al, 2008; Moseley et al, 2002). have questioned the usefulness of arthroscopy as a treatment for KOA to the point that some scientific associations considered these trials to be a reference for advising against arthroscopic surgery with lavage and/or debridement in patients with primary symptomatic KOA (Jevsevaar, 2013). The available information concludes that arthroscopic surgery is not a treatment of choice in patients with primary KOAalone. However, it must be taken into account that over 90% of patients with symptomatic KOA have a magnetic resonance image (MRI) compatible with meniscal pathology (Bhattacharyya et al, 2003). Therefore, arthroscopic surgery would be indicated in those patients with meniscal or mechanical symptoms presenting a concomitant diagnosis of KOA, and the suitable choice of patients that can benefit from this technique plays an important role (Karpinski et al, 2019).

Viscosupplementation with hyaluronic acid (HA) has been used successfully over the past 2 decades for the treatment of KOA and other joints in patients who do not suitably respond to non-pharmacological, conservative treatments or to simple analgesics, such as paracetamol (Zhang et al, 2008). Its efficacy is supported by a number of clinical trials, post-authorisation studies and various meta-analyses (Waddell and Bert, 2010; Maheu et al, 2019).

Viscosupplementation has also been used as an alternative treatment to delay arthroscopic surgery (Delbarre et al, 2017; Altman et al, 2015; Maheu et al, 2019). In other cases, it has been used to lubricate the joint and as replacement for synovial fluid lost during the intervention. Lastly, the administration of HA after arthroscopic surgery has also been used and has yielded good results because of its analgesic effect, since pain may persist after the intervention (Huskin et al, 2008; Waddell and Bert, 2010).

The published clinical trials (Mathies, 2006; Hempfling, 2007; Thein et al, 2010; Uluçay et al, 2007; Huskin et al, 2008; Atay et al, 2008; Heybeli et al, 2008; Westrich et al, 2009; Chau et al, 2010; Hamawandi, 2021) studying the efficacy of arthroscopic surgery associated with the administration of HA, conclude that combined treatment is effective, relieves post-surgical pain and aids in a faster recovery. However, there is still no consensus as to the administration regimen for HA. The present paper summarises the findings of the evaluation of a case series of patients treated by a working group of specialists in Orthopaedics in the context of their regular clinical practice. The objective was to explore different dose regimens of HA as an adjuvant therapy to alleviate pain after arthroscopic surgery and to reach conclusions that could be of use for the scientific community.

Materials And Methods:-

This was a prospective observational evaluation of a case series of patients treated by specialists in Orthopaedics from several Latin American countries and from Spain, in the context of their regular clinical practice and conducted in accordance with the principles of Good Clinical Practice.

The study population included adult subjects with an indication of arthroscopic surgery of the knee presenting meniscal injury and/or the presence of free bodies and where OA could be present. Patients could not be selected if they had a body mass index >35 kg/m^2, varus-valgus malalignment above 5^o with respect to physiological valgus, unstable knee, associated mosaicplasty, chondrocyte grafting, scaffolding or Platelet Rich Plasma (PRP), or meniscal suture or transplant. Type of surgery, surgical manoeuvres and procedures on the cartilage were recorded, as well as the extension and Outerbridge grade of chondral injuries in the tibia, patella and femur.

Three weeks after arthroscopic surgery, patients were randomly allocated to receive one single intra-articular injection of 5 ml of HA (Group 1) or three intra-articular injections of 2.5 ml of HA each with weekly intervals (Group 2). The same HA product was used in all patients: a formulation of sodium hyaluronate obtained by fermentation, with an

intermediate molecular weight (average 900 kDa), and a concentration of 10 mg/ml presented in prefilled syringes. Follow-up visits were performed at 3 and 6 months after treatment by the same physician who administered the treatment. The efficacy of the treatment was assessed as reduction in pain and improvement in function using a 0-100 mm Visual Analogue Scale (VAS) (the higher the score, the worse the condition) at 3 and 6 months post-treatment vs. post-arthroscopy values. Patient satisfaction was also recorded. From a safety point of view, the occurrence of adverse events was monitored.

A sample size of 75 patients was considered sufficient to achieve the objectives of the study. The main population for analysis was the Intention to treat (ITT), composed of those patients that received at least one dose of HA and had at least one evaluation post-treatment. The following descriptive statistics was used: mean and standard deviation plus range for quantitative variables and percentages for qualitative variables. The Kolmogorov-Smirnoff test was performed to show data normality. For comparative statistics, the t-test was used for comparisons of means for independent groups and the paired t-test was used for comparisons of means for dependent or paired groups. For non-normally distributed variables the Student's t-test for independent samples or the Mann-Whitney test were used. Chi^2 test or Fisher's exact test were used for comparison of proportions. A logistic regression analysis was performed using the pain reduction or function improvement variables at 3 and 6 months as a dependent variable, with changes of 10, 20 or 30 mm or 10, 20 and 30 %.

The data were analysed using SPSS V14 (SPSS Inc, Chicago Il) and the statistical significance was set at 0.05.

Results:-

The ITT population was composed of 75 patients that received at least one dose of HA and had at least one evaluation post-treatment. The distribution of patients is shown in Figure 1.

The groups were homogeneous in terms of demographic characteristics, comorbidities and pathology at the baseline that are shown in Table 1. The white race was the most common (60.0%), women represent 56 % of the sample and the mean age was 50.2 years.

Previous treatments that were more frequently prescribed for KOA were NSAIDs (50.7%) and physiotherapy (36.2%) with no differences between groups. There were no differences in the type of surgery, associated gestures or other procedures performed during the intervention (Table 2). Partial medial meniscectomy was the most common intervention followed by partial lateral meniscectomy or both. Debridement was the most common associated surgical manoeuvre recorded, followed by abrasion and microfracture. There were also no differences between the groups with respect to the location, extension and Outerbridge grade of the femoral, tibial or patellar injuries.

Compared to pre-arthroscopy values, statistically significant improvements ($p<0.001$) were found at 3 weeks (prior to intra-articular treatment) and at 3 and 6 months with pain reductions of 37.8%, 64.7% and 77.6% in Group 1; and 41.2%, 62.5% and 83.4% respectively in Group 2. Similarly, improvements found in function were of 17.13%, 68.2% and 80.5% in Group 1 and 23.5%, 52.2% and 77.3% respectively in Group 2 (Figure 2a and 2b). When pain and function values at 3 and 6 months were compared with the values at 3 weeks post-arthroscopy, the improvement observed was statistically significant in both groups ($p\leq0.001$). Nevertheless, there were no differences between the groups in any of the parameters analysed. The patients rated the treatment as excellent.

On an exploratory basis, efficacy was analysed in terms of percentage of patients (responders) presenting an absolute reduction (10 mm, 20 mm, 30 mm) and/or relative reduction (10%, 20%, 30%) of pain and function at follow-up with respect to pre-arthroscopy and 3 weeks post-arthroscopy values. The results showed that there were no statistically significant differences between both treatment groups in the percentage of responders for any of the absolute or relative reduction cut-off points.

A total of 50.7% of the patients used NSAIDs when they entered the study (pre-arthroscopy). With the data obtained at 3 and 6 months, it was observed that the use of NSAIDs (including paracetamol) dropped throughout follow-up in both treatment groups.

No adverse events were recorded during the study nor were any comments related to the safety of the treatments administered.

Discussion:-

Arthroscopic surgery is a commonly applied technique in traumatology, and the knee joint is where this technique is most commonly used. Although arthroscopy per se is not currently considered a treatment of choice for OA, the majority of patients with symptomatic KOA have evidence of meniscal and/or articular surface pathology (Waddell and Bert, 2010), and over 90% of patients with KOA have an MRI compatible with meniscal tears (Bhattacharyya et al, 2003). As such, arthroscopic surgery would be indicated in those patients with meniscal or mechanical symptoms presenting a concomitant diagnosis of KOA. In this sense, recently the American Academy of Orthopaedic Surgeons (AAOS) recommended the use of arthroscopic partial meniscectomy for the treatment of meniscal tears in patients with concomitant mild to moderate OA who have failed physical therapy or other nonsurgical treatments (American Academy of Orthopaedic Surgeons. Management of Osteoarthritis of the Knee, Clinical Practice Guideline, 2021).

During arthroscopy, irrigation fluid helps to remove the debris, but it can contribute to the loss of synovial fluid of the joint; with this loss, the concentration of HA decreases, having a negative impact on the metabolism and structure of the joint cartilage (Bulstra et al, 1994; Cuellar et al, 2016; Kohlhof et al, 2016; Bigoni et al, 2017). On the other hand, after knee arthroscopy patients experience pain and function impairment and it has been described that the analgesics used to control pain can result in adverse events (Talu et al, 2002; Gonzales et al, 2016).

Published clinical trials administered viscosupplementation in both immediate and late post-surgery (Shen et al, 2018). Therefore, there is no consensus as to when viscosupplementation should be used or about the dose regimen, although it should be noted that the most recent trials opted administering viscosupplementation at 2-3 weeks post-arthroscopy or even later (Trueba-Vasavilbaso et al, 2017; Hamawandi et al, 2021; Başar et al, 2021; Saw et al, 2021). At 2-3 weeks after arthroscopy, the exudation caused by the surgical procedure stops (Yang et al, 2021); at this time, the administration of HA in the operated joint contributes to pain relief with long lasting effects. HA also improves biological function of synovial membrane and prevents further destruction and disappearance of the cartilage matrix (Yang et al, 2021). The posology of HA to be followed is also a matter of discussion.

Previous published data confirmed the efficacy of this HA product when used in multiple injections after arthroscopic surgery (Trueba-Vasavilbaso et al, 2017). The present study was conducted to explore the possibility of using single injection HA compared to multiple injections to simplify the procedure but maintaining therapeutic efficacy. One group received three injections (2.5 ml each) at weekly intervals while the other was tested with one shot regime (5 ml). In both groups, the treatment started at 3 weeks post-surgery.

Both groups were homogeneous with respect to demographics and baseline characteristics, and there were no differences concerning the type of surgery, associated surgical manoeuvres or other procedures performed during the intervention. Partial medial meniscectomy was the most common intervention followed by partial lateral meniscectomy or both. Debridement was the most common associated surgical manoeuvre recorded, followed by abrasion and microfracture. There were also no differences between the groups with respect to the location, extension and Outerbridge grade of the femoral, tibial or patellar injuries.

The efficacy results in both groups at follow-up in terms of pain reduction and joint functionality showed significant improvements at 3 weeks, and 6 months post-treatment vs. pre-arthroscopy values. It is important to note that the improvements in pain and function at 3 and 6 months increased and were statistically significant and better compared to those at 3 weeks after arthroscopy (before intra-articular treatment), thus confirming the efficacy of the HA treatments administered although there were no differences between groups. The degree of patient satisfaction at 6 months post-treatment was very high and with no differences between groups.

The 50.7% of the patients used NSAIDs when they entered the study (pre-arthroscopy). With the data obtained at 3 and 6 months, it was observed that the use of NSAIDs (including paracetamol) dropped throughout follow-up in both treatment groups. No statistically significant differences with respect to the use of concomitant medication at 3 and 6 months was detected between groups.

On an exploratory basis, efficacy was analysed using different cut-offs in terms of percentage of patients (responders) presenting absolute and/or relative improvement of pain and function with respect to both pre-arthroscopy and 3 weeks post-arthroscopy values. No statistically significant differences were detected at any of the cut-offs used.

The limitations of this study include that both researchers and patients were not kept blind due to the different number of injections on each group and a potential bias in the results could not be disregarded. The use of rescue medication might affect the accuracy of the clinical improvement although a logistic regression analysis performed indicated that the use of concomitant medication had no influence on the assessment of the efficacy of HA treatments. Only VAS for efficacy evaluation was used, with the intention of reproducing the real clinical practice as much as possible, although it would have been interesting to use a more complex index like WOMAC. The study did not use a control group with placebo or surgery alone; however, the superiority of HA over placebohas been recognised (Miller et al, 2013; Bannuru et al, 2015; Trojian et al, 2016). With reference to the presence of a non-treated arm, we compared our results with those of published studies that included a "surgery-alone" group and used similar efficacy variables (Heybeli et al, 2008, Katz and Losina, 2013) to ours; the improvement rates in our study are significantly higher than those obtained in the mentioned control groups suggesting that efficacy rates using HA after arthroscopy are higher than arthroscopy alone.

As regards the safety of HA, no adverse events were recorded while the study was being performed nor were there any comments affecting the safety of the treatments reported, suggesting that both dosage regimens have similar safety profiles.

The meta-analyses published confirmed the efficacy of the combination arthroscopy plus viscosupplementation regardless of the time of administration or the volume of HA administered (Shen et al, 2018; Yang et al, 2021) and it can be considered that there is sufficient data to affirm that HA can be used in both immediate and late post-surgery with good results in terms of pain relief and improvement of joint function. Protocols have been proposed for the use of HA in patients after arthroscopy (Waddell and Bert, 2010). These protocols are mainly based on the analysis of intraoperative findings: presence of OA, Outerbridge grade, etc., which may make viscosupplementation advisable either immediately after-surgery or leaving the joint at rest and waiting 2-3 weeks for administration if pain has not subsided. In our study, the viscosupplementation in late post-arthroscopy achieved a significant reduction of pain and improvement in function with no differences between the dosage regimens studied. In our experience, reducing pain in the postoperative period improves adherence to rehabilitation and, in the long run, the use of NSAIDs is reduced in addition to avoiding chronic pain due to OA. One shot with HA could be considered a safe and effective option as an adjuvant treatment in arthroscopic surgery, favouring a better recovery with a lower cost for both the patient and the Healthcare System, although further controlled trials should be of interest.

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ArthroscopyWorkingGroup

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Figure 1:- Distribution of patients.

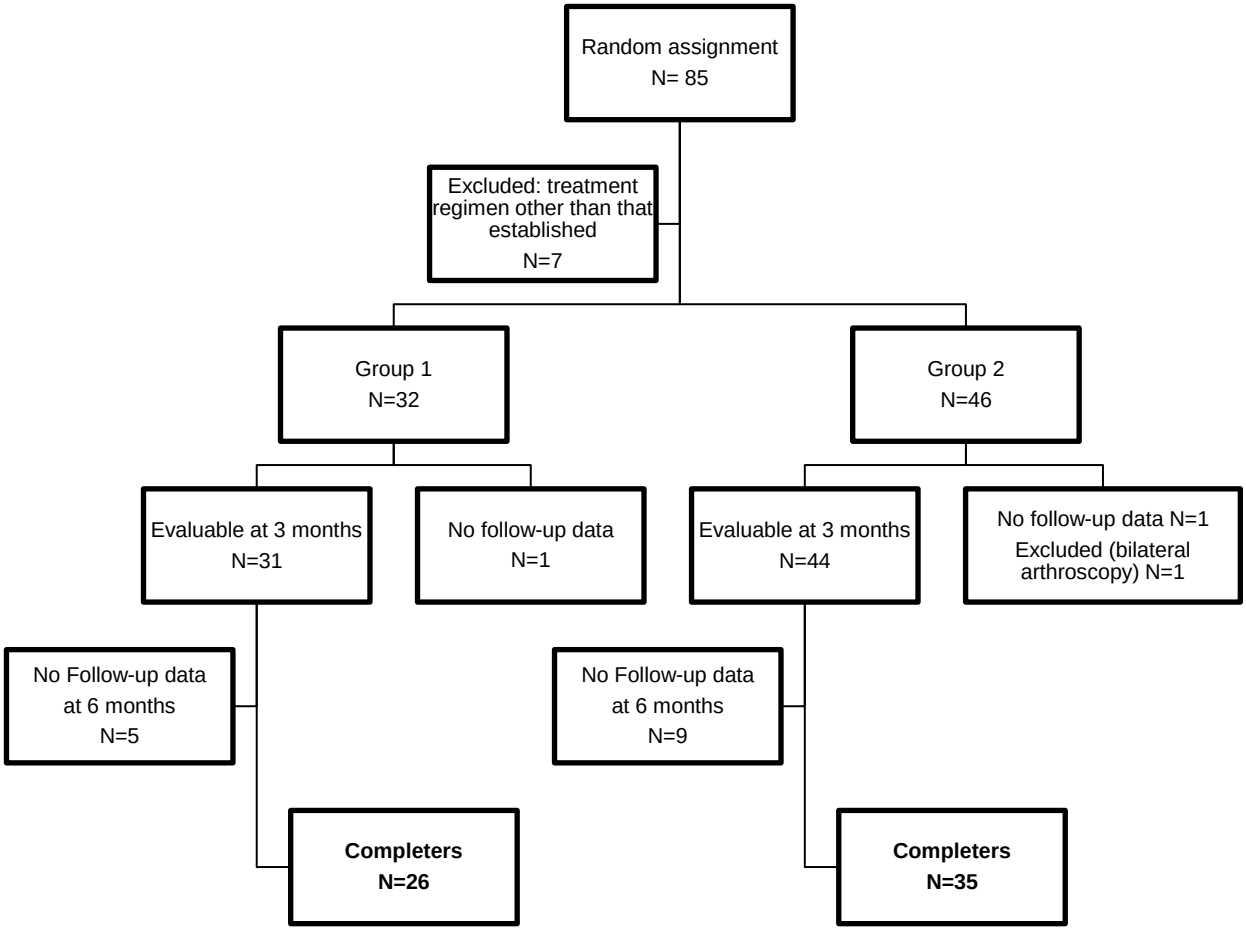


Table 1:- Demographic and baseline characteristics.

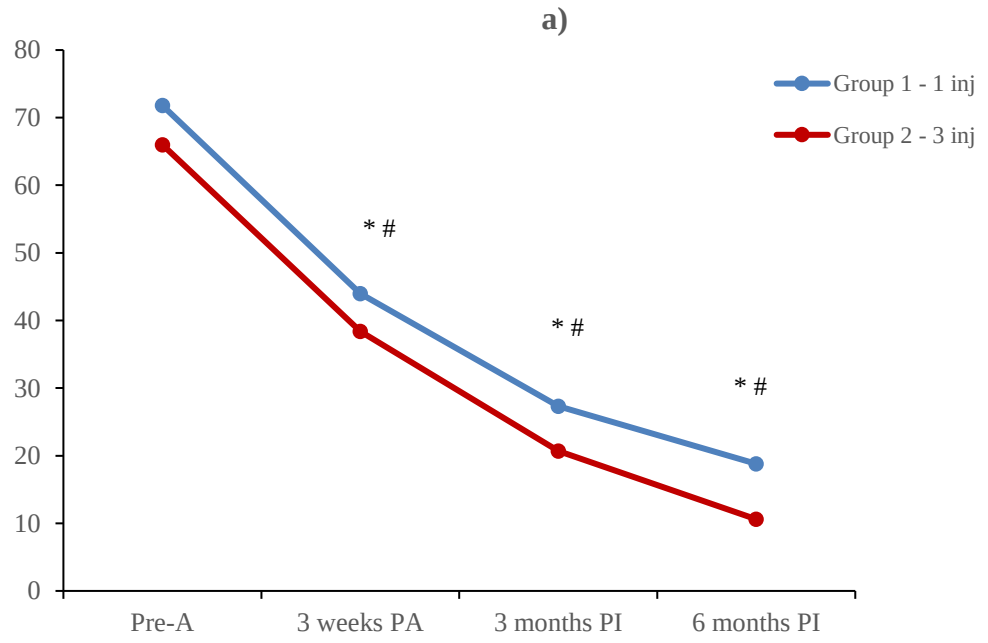
	Group 1 N=31	**Group 2 N=44**	**Total N=75**
Age, mean (SD)	54.13 (16.8)	47.50 (12.5)	50.24 (14.7)
Gender (female), N (%)	21 (67.7)	21 (47.7)	42 (56.0)
Race, N (%)			
White	18 (58.1)	27 (61.4)	45 (60.0)
Mestizo	11 (35.5)	14 (31.8)	25 (33.4)
Black	0 (0.0)	1 (2.3)	1 (1.3)
Missing	2 (6.5)	2 (4.5)	4 (5.3)
Clinical history, N (%)			
None	21 (67.7)	36 (81.8)	57 (76.0)
Allergy	1 (3.2)	0	1 (1.3)
Cardiopathy	0	1 (2.8)	1 (1.3)
Arterial hypertension (AHT)	6 (19.4)	3 (6.8)	9 (12.0)
Diabetes	2 (6.5)	0	2 (2.7)
Dyslipemia	3 (9.7)	1 (2.3)	4 (5.3)
Hypothyroidism	2 (6.5)	1 (2.3)	3 (4.0)
Findings N (%)			
Osteoarthritis	5 (16.1)	13 (29.5)	18 (24)
Pain	19 (61.3)	21 (47.8)	40 (53.4)

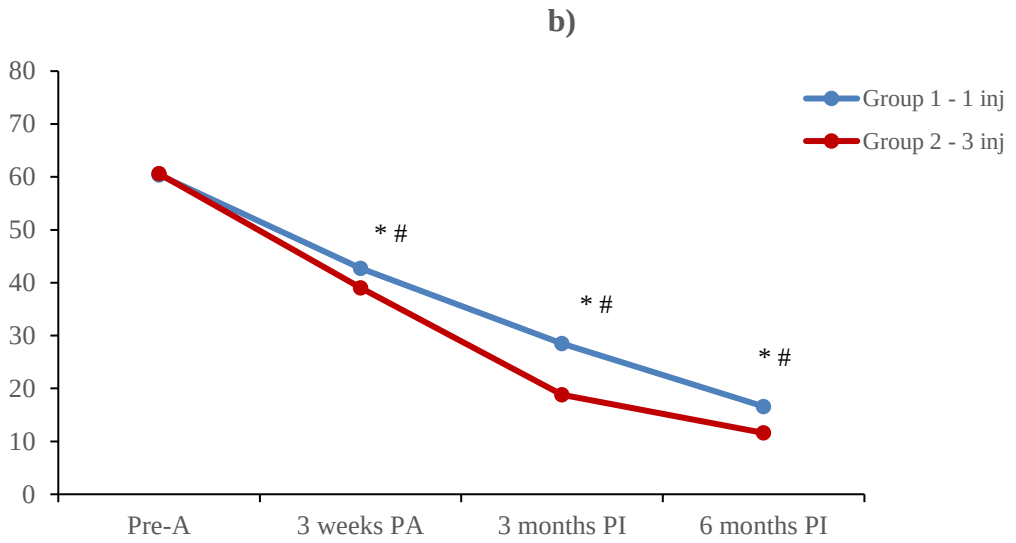
Stiffness	2 (6.5)	6 (13.6)	8 (10.7)
Meniscal syndrome	11 (35.5)	13 (29.5)	24 (32.0)
Others	6 (19.4)	3 (6.8)	9 (12.0)
Pain at baseline (VAS, mm) (Mean, SD)	71.8 (16.6)	66.0 (19.6)	68.4 (18.5)
Function at baseline (VAS, mm) (Mean, SD)	60.4 (21.6)	60.6 (21.5)	60.5 (21.4)

Table 2:- Surgery.

Variable	Group 1 N=31	Group 2 N=44	Total N=75	p
Type of surgery N (%)				
Partial lateral meniscectomy	5 (16.2)	10 (22.7)	15 (20.0)	0.481
Partial medial	20 (64.5)	20 (45.5)	40 (53.3)	0.103
Partial medial + partial lateral	3 (9.7)	4 (9.1)	7 (9.3)	1.000
Lateral subtotal	0	3 (6.8)	3 (4.0)	0.262
Partial medial and subtotal	0	1 (2.3)	1 (1.3)	1.000
Medial subtotal	0	1 (2.3)	1 (1.3)	1.000
Not described	3 (9.7)	6 (13.6)	9 (12.0)	0.728
Associated surgical procedure N (%)				
Debridement	23 (74.2)	32 (72.7)	55 (73.3)	0.888
Abrasion	5 (16.1)	15 (34.1)	20 (26.7)	0.083
Microfracture	5 (16.1)	7 (15.9)	12 (16.0)	1.000
Perforation	1 (3.2)	2 (4.5)	3 (4.0)	1.000
Other procedures N (%)				
Synovectomy	13 (41.9)	21 (47.7)	34 (45.3)	0.620
Suture	0	1 (2.3)	1 (1.3)	1.000
ACL tightening	2 (6.5)	2 (4.5)	4 (5.3)	1.000
Realignment	0	1 (2.3)	1 (1.3)	1.000
Plica	3 (9.7)	1 (2.3)	4 (5.3)	0.300
Removal of foreign body	7 (22.6)	12 (27.3)	19 (25.3)	0.645

Figure 2:- Comparison of the differences in **a)** painand **b)** function along the study vs baseline.





Pre-A: pre-arthroscopy; PA: post-arthroscopy; PI: post-injection
P<0.001: *Group1; # Group 2 vs Pre-A

Data Availability
The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure
The results of this study were partially presented as a poster at the 2019 Congress of Pan American League of Associations for Rheumatology (PANLAR).

Conflicts Of Interest
The authors declare that they have no conflicts of interest regarding the publication of this paper.

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