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RESEARCH ARTICLE

EFFECTIVENESS OF INTRA-ARTICULAR HYALURONIC ACID ON PATIENTS SUFFERING FROM PAINFUL SHOULDER

Carolina Pisanti[1], Juan Valles[1], Mª Pilar Coronel[2] and Carlos Gavín[3]

1. Hospital Ortopédico Infantil de Caracas. Av. Andrés Bello, Caracas 1050, Distrito Capital, Venezuela.
2. Meiji Pharma Spain S.A. Avda de Madrid 94, 28802 Alcalá de Henares, Madrid, Spain.
3. Hospital Universitario Fundación Alcorcón. Calle Budapest, 1, 28922 Alcorcón, Madrid, Spain.

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Abstract

This work was a retrospective, observational study to analyse the effectiveness of viscosupplementation in terms of pain relief and function improvement in a cohort of patients suffering from shoulder pain and treated under usual clinical practice conditions. The population included patients with painful shoulder, stiffness grades I/II and intact rotator cuff or with partial thickness tear. Previous hyaluronic acid or corticosteroid injections, passive mobilization or shoulder infections were not permitted. Patients received 3-5 injections of medium molecular weight hyaluronic acid and efficacy was assessed at the end of treatment and at 3 and 6 months. Effectiveness was evaluated using the Constant scale, physician and patient global assessments. In total 180 patients were analysed with a mean age of 49.1 years and 52.2% were female. More than 50% presented 2 relevant symptoms, being pain present at baseline in 82.2% followed by stiffness (57.2%) and instability (5.6%). Mean Constant value was 53.8 points. A mean improvement of 14.3 points was observed at the end of treatment, 28.2 at 3 months and 37.9 at 6 months ($p<0.001$ versus baseline at all-time points). Constant condition at the end of treatment was excellent in 3.3% of patients, good in 70.6% and fair in 26.1% whereas at 6 months it was excellent in nearly 100% patients in agreement with patient and physician assessments. These results suggest that viscosupplementation constitute a conservative and minimally invasive approach to manage shoulder pain with effects lasting for at least 6 months.

Introduction:-

Shoulder disorders are recognised as a disabling problem that affects daily functioning and working ability of the individuals leading to a substantial economic burden. Estimates of the cumulative annual incidence vary from 7-25% in Western general population with a peak in the age category of 42-46 years (Roy et al, 2018). The underlying aetiologies include glenohumeral osteoarthritis, rotator cuff tear, tendinitis, adhesive capsulitis and subacromial bursitis (Linaker and Walker-Bone, 2015). Stiff shoulder is a global term that should be used to describe a patient with a restricted range of motion which is the sum of a premorbid state, the initial injury, the response and the

Corresponding Author:- Mª Pilar Coronel
Address:- Meiji Pharma Spain S.A. Avda de Madrid 94, 28802 Alcalá de Henares, Madrid, Spain.

secondary changes that occur with time (Itoi et al, 2016). The appropriate diagnosis is based on physical history, clinical examination and image techniques like X-ray and magnetic resonance image (MRI).

Damage or dysfunction affecting one component of the shoulder can lead to secondary pathological changes contributing to persistent pain (Burbank et al, 2008; Andrews, 2005). In fact, pain is the primary complaint within the early stages and conservative treatment is the primary choice. Although there are no standardized protocols to control shoulder pain and the options described in the literature are diverse, physical therapy, oral analgesics nonsteroidal-anti-inflammatory drugs (NSAIDs) and intra-articular injections are commonly used (Linaker and Walker-Bone, 2015; Itoi et al, 2016). There is some evidence for modest benefit of physiotherapy for shoulder pain at short-term (Green et al, 2003). Analgesics and NSAIDs are not always effective; particularly NSAIDs due to their vascular and gastro-intestinal toxicity (Bhala et al, 2013) and may be associated with substantial side effects when taken for long durations and among the elderly (Wongrakpanich et al, 2018).

In chronic shoulder pain the glenohumeral joint will nearly always be involved, making intra-articular therapy a reasonable approach to consider (Andrews, 2005). Shoulder injections of corticosteroids are a treatment option commonly used although systemic adverse events can be expected and precautions should be observed in patients with concomitant diseases such as hypertension or diabetes (Younes et al, 2007; Choudhry et al, 2016). Besides, there is some evidence suggesting that repeated injections may cause tendon damage (Metcalfe et al, 2009; Dean et al, 2014).

The administration of hyaluronic acid (HA) exerts a mechanical effect providing lubrication of the joint and restoring the rheological properties of the synovial fluid (Balazs and Delinger, 1993). In addition, several studies have confirmed that HA interacts with mediators of inflammation, reduces apoptosis in osteoarthritic cartilage, stimulates chondrocyte growth and the synthesis of extracellular matrix proteins (Yu et al 2014; Peng et al, 2010; Waddell et al 2007) and inhibits nociceptive receptors of pain (De la Peña et al, 2017). Therefore, the intra-articular injection of HA can have a beneficial effect on pain relief and function improvement at multiple levels and in several aetiologies of shoulder pain that have some degree of intra-articular disease (Andrews, 2005).

The effectiveness of HA to treat knee osteoarthritis has been confirmed through extensive clinical evidence and viscosupplementation is currently recommended by several scientific societies (Trojian et al, 2016; Hochberg et al, 2012; Bruyère et al, 2019; Conrozier et al, 2018). However, the efficacy of HA to treat shoulder pain is somewhat not as clearly established resulting from the variety of disorders possible and due to data from literature show sometimes contradictory results (Blaine et al, 2008; Kwon et al,2013; Lee et al, 2015; Chou et al,2010; Saito et al, 2010). In this context the objective of the present study has been to analyse the effectiveness of viscosupplementation in terms of pain relief and function improvement in a retrospective cohort of patients suffering from shoulder pain and treated under conditions of normal clinical practice.

Materials And Methods:-

This was a retrospective, observational evaluation of a cohort of patients treated in a single clinic. The project was approved by the Ethics Review Board of the Fundación del Hospital Ortopédico Infantil (Caracas, Venezuela).

The study population included patients with painful shoulder of at least 6 months of evolution, stiffness grades I/II (Reeves, 1975), MRI available, with rotator cuff intact or with partial thickness tear and at least 6 months follow-up. Patients could not be included if they had received previous administration of HA in the shoulder, infiltration of corticosteroids in the previous year, history of infection in the shoulder or previous passive mobilization with or without sedation. Each patient received at weekly intervals 3-5 intra-articular injections of SUPRAHYAL®/ADANT® (MEIJI PHARMA SPAIN S.A.), a hyaluronic acid obtained from fermentation, non-crosslinked, and 1000 kDa molecular weight. The administration was always made using the posterior approach. In case the HA injection could not be administered in the same day, a single block with lidocaine, bupivacaine and Ringer lactate was administered for temporary pain relief.

Follow-up visits for effectiveness and safety assessments were performed at the end of treatment (EOT) and at 3 and 6 months by the same physician who administered the treatment. Effectiveness was assessed using the Constant scale (Constant and Murley, 1987) and patient's condition was classified as excellent (≥80 points), good (65-79 points), fair (50-64 points) or poor (<50 points) (Becerril-Bautista et al, 2014). The magnitude of change in the Constant scale was also analysed. The patient's condition (excellent, good, fair, poor) at different time points was

classified according to following patterns of change: worse (move from one category to another lower, e.g. from fair to poor), no change, and improvement (change to a better category). Physician and patient global assessments were ratted using a Likert scale of five categories (much better, better, fair, poor, much poor). For safety purposes the patients were asked at follow-up visits about any adverse event that might have occurred and they could also contact the physician at any time.

The following descriptive statistics were used: mean and standard deviation plus range for quantitative variables and percentages for qualitative variables. Kolmogorov Smirnoff test was performed in order to show data normality. For comparative statistics t-test was used for comparisons of means for independent groups and t paired test for comparisons of means for dependent or paired groups. For non-normally distributed variables Mann-Whitney test was used. ANOVA test was used for comparisons of more than two groups. Data were analysed using SPSS V14 (SPSS Inc, Chicago Il) and the statistical significance was set at 0.05.

Results:-

A total of 180 consecutive patients that met the study requirements were treated in our clinic between October 2004 and October 2017 forming the full set for analysis. Mean age was 49.1 years, 74.4% of white race and 52.2% were female. Hypertension was the most frequent comorbidity (38.9%) followed by diabetes (23.3%) and endocrine disorders (8.3%). A total of 15.0% (n=27) practice any sport activity. Right shoulder was affected in 61.1% of the cases and more than 50% presented 2 relevant symptoms, being pain present in 82.2% of the cases followed by stiffness (57.2%) and instability (5.6%) (Table1). As detailed in Table 2 most frequent findings in MRI included partial articular side tear of the rotator cuff (PASTA) (n=66), superior labral tear from anterior to posterior (SLAP) (n=57), laxity (n=55) and calcific tendinitis (n=32).

Patients received intra-articular treatment with HA at weekly intervals. In total 155 patients (86.1%) received 3 injections whereas 25 (13.9%) received 5 injections.

Mean value in Constant scale at baseline was 53.82 points. A mean improvement of 14.3 points was observed at the EOT, 28.2 points at 3 months follow-up and 37.9 at 6 months ($p<0.001$ vs baseline at all-time points).

At the EOT, the global condition in Constant was graded as excellent in 6 patients (3.3%) good in 127 (70.6%) and fair in 47 (26.1%). At 6 months follow-up, global condition was excellent in 179 (98.9%) out of 180 patients.The response based on each one of the findings in MRI (finding present/absent) was analysed and no significant differences were found in Constant values between baseline, EOT or the follow-up visits ($p>0.05$ for all comparisons). Some differences in Constant values were found at the EOT and at 3 months ($p<0.01$ vs baseline) between patients that received 3 injections or those receiving 5 in favour of 3 injections group.

The magnitude of change in Constant scale is shown in Table 3. Accordingly, at 3- and 6-months follow-up patients related to feel much better fully in agreement with physician assessments as shown in Table 4.

A total of 135 patients received a block in the previous days to HA administration. From them 103 cases were due to the presence of stiffness. Some other cases due to a temporary unavailability of the HA treatment (n=32). Each patient received the block only once and it was administered at least 3 weeks before the HA injection. Between patients that received a block or those that did not receive it (n=45) there were statistically significant differences in Constant values at EOT ($p=0.041$) but not at 3 months ($p=0.862$) or 6 months ($p= 0.210$).

Some concomitant treatments were used during the study. In total 88% of the patients received physical therapy and at and follow-up visits, responder rates did not show differences between groups (p=1,000 at 3 months; p=NC at 6 months). Concomitant treatment with NSAIDs (68%) achieved better response rates at 3 months ($p=0.027$) but not at 6 months (p=NC).

No adverse events were reported during the administration of the product or during follow-up.

Discussion:-

Affections of the shoulder are a common cause of chronic pain and contribute to loss of productivity and high social costs (Andrews, 2005). The pathologies associated to painful shoulder may be diverse, but all of them share the

presence of pain and impaired function, being the relief of pain the target of the treatment as well as the quick return to daily activities including sport practice.

Viscosupplementation for knee OA has become a common practice and its effectiveness has been demonstrated in a broad variety of clinical trials, systematic reviews and meta-analysis. Interesting is also to remark the favourable safety profile of this product compared to other existing therapeutic options (Bannuru et al, 2016; Bannuru et al, 2015; Miller and Block 2013). It is also used in other joints and several studies using HA to treat chronic shoulder pain have been documented (Blaine et al, 2008; Kwon et al, 2013; Lee et al, 2015; Chou et al, 2010; Saito et al, 2010), although its efficacy has not been clearly established and the results some times vary probably due to the diversity of individual pathologies. As a result, there are not clinical guidelines that address to the non-operative management of shoulder pain when considered as a clinical entity (Lin et al, 2018). The primary objective of the present work was to analyse the effectiveness and safety of intra-articular injections of HA for the treatment of patients coming to our clinic suffering from painful shoulder due to multiple and sometimes overlapping aetiologies. In our case clinical examination together with MRI was considered the best combination to reach an appropriate diagnosis.

It could be argued that X-ray remains the first imaging test to be performed in the investigation of any shoulder pain due to its wide availability and ready accessibility (Hershkovich et al, 2014; Tuite and Small,2017) providing useful information particularly in cases with a history of trauma but this technique provides limited information on the soft tissue structures around the shoulder (King and Healy, 1999); on the other hand, the use of ultrasound is growing but it has a number of limitations and varying reports questioned its accuracy (King and Healy, 1999). As a consequence, MRI is becoming the first line diagnostic modality for shoulder pain (Hershkovich et al, 2014; Tuite and Small, 2017).

In our study, all the injections were administered by the same clinician, a shoulder specialist with years of experience. The injections were administered without ultrasound guidance. Different reviews have been published regarding the effectiveness of non-guided administration at the shoulder compared to imaging guidance with different results. Whereas some stated there was not enough evidence to recommend ultrasound guided injections over non-guided ones (Tuite and Small, 2017; Bloom et al, 2012) others concluded that image-guided were more accurate and efficacious (Daniels et al, 2018). Nevertheless, the consensus exists about the fact that accuracy of non-guided injections relies on the experience of the well-trained physician to administer the medication into the correct place (Daniels et al, 2018; Gyftopoulos et al, 2018).

Among our patients mean value in Constant scale at baseline was in the lower limit of fair condition and a significant improvement was observed at the EOT, which increased at 3 months and persisted at the end of follow-up. It is interesting to note that more than 95% of the patients experienced an improvement of ≥2 categories in Constant scale. In the context of a clinical study, the use of reliable and valid outcome measures to evaluate the effects of a given treatment is important, but sometimes these scores do not provide a clear idea of how effective a treatment is and how many patients have a clinically relevant therapeutic response to treatment (Salottolo and Sthal, 2018). The concept of the minimal clinical important change (MCIC), defined as the smallest change in a score that a patient would perceive as important (Christiansen et al, 2015), is a useful tool to assess treatment outcome for shoulder. It is estimated from the results obtained in the Constant scale although to now it has been sparsely evaluated. Applying to our study the 11 points cut off established by Christiansen et al (Christiansen et al, 2015) the 100% of the patients in our study exceed the MCIC at 3 months after treatment and these results persist after the 6-months follow-up.

No standardized protocols for HA in shoulder are available in clinical practice to give clear recommendations for treatment. In our study 86% of the patients received 3 injections instead of 5 being the economic reasons the main cause. Curiously some differences in Constant values were found at the end of treatment and at 3 months in favour of the 3 injections group ($p<0.01$) vs 5 injections but these differences were considered not clinically relevant due to absolute values are small and the lack of differences found at the end of follow-up.

During the study there were no dropouts. To our opinion this fact is due to cultural reasons: the patient fully relies on the doctor and this confidence is supported by the good results of the treatment administered. The good safety profile of HA is well known and this study was not an exception: the treatment was well tolerated and no adverse events were noted during the administration or the follow-up.

This work has some limitations that should be addressed. This is a retrospective study where the cases treated in a single clinic were studied and it lacks of control group.

The treatment was administered and evaluated by the same physician and this could be regarded as a risk of bias for the evaluation of the results. Bias is always possible. Nevertheless, we consider that this risk is higher when considering a prospective controlled study where the administrator and evaluator are the same person and is aware of the treatments administered. The present work is a retrospective analysis of the data already existing in our database that reflect the reality of clinical setting where the same physician administers the treatment and evaluates the patient.

In the previous weeks to HA treatment, a 75% of our patients received a single block with lidocaine + bupivacaine + Ringer lactate due to stiffness in most cases (76%). We used the block to achieve a temporary relief of pain that would allow a mobilization of the shoulder avoiding the risk of extravasation when administering HA. In the remaining cases the block was administered due to a temporary unavailability of the HA treatment. In all the cases it was administered at least 3 weeks in advance so as not interfere with HA. We analysed the outcomes of block /no block patients and significant differences between groups were not found.

The lack of image guidance may be also argued as a limitation of the study. All the injections were administered by the same well experienced physician and the results endorse the appropriateness of the administration in accordance with literature data.

Considering similar response to either 3 or 5 injections was obtained, together with a lower cost and number of visits, it could be argued in favour of using shorter regimens; nevertheless, the efficacy at long term is a question that remains to be answered and in this sense our follow-up of 6 months could have not been sufficient.

The efficacy of viscosupplementation to treat painful shoulder has been already described and the results shown herewith go in the same direction. Nevertheless, important questions like the number of injections, time to re-injection and the best profile of patients that can benefit of this treatment remain to be properly answered.

Table 1:- Demographics and baseline condition.

Age, mean (sd)	49.1 (17.5)
Gender (female)	94 (52.2%)
Race	
White	134 (74.4%)
Black	20 (11.1%)
Mestizo	26 (14.4 %)
Clinical history	
Hypertension	70 (38.9%)
Diabetes	42 (23.3%)
Endocrine	15 (8.3%)
Asthma	14 (7.8%)
Rheumatoid arthritis	7 (3.9%)
Dyslipemia	8 (4.4%)
Cancer	4 (2.2%)
Blood presure, mean SBP(sd)/DBP(sd)	129.3 (16.2)/ 80.9 (9.4)
Symptoms	
Pain	148 (82.2%)
Stiffness	103 (57.2%)
Instability	10 (5.6%)
Relevant symptoms	
1 symptom	79 (43.9%)
2 symptoms	91 (50.6%)
missing	10 (5.6%)
Previous trauma	71 (39.4%)
Right shoulder	110 (61.1%)

Table 2:- Findings in MRI (More than one finding possible).

PASTA	66 (27.5%)
SLAP	57 (23.7%)
Laxity	55 (22.9%)
Calcific tendinitis	32 (13.3%)
Osteoarthritis	12 (5.0%)
Previous trauma	9 (3.7%)
Buford	3 (1.25%)
KIM	3 (1.25%)
Bankart	2 (0.8 %)
Hill-Sachs	1 (0.4%)

Table 3:- Magnitude of change in Constant scale

	Change n (%)		
	Baseline vs EOT	**Baseline vs 3 months**	**Baseline vs 6 months**
Worse	2 (1.1%)	0 (0.0%)	0 (0.0%)
No change	34 (18.9%)	1 (0.6%)	0 (0.0%)
Improv. 1 category	103 (57.2%)	6 (3.3%)	8 (4.4%)
Improv. ≥ 2 categories	41 (22.8%)	173 (96.1%)	172 (95.6%)

p <0.001between columns 1 and 2
p <0.001between columns 1and 3
p=0.155 between columns 2 and 3

Table 4:- Patient and physician assessments.

	3 months		**6 months**	
	Patient	**Physician**	**Patient**	**Physician**
Much better	46 (25.6%)	26 (14.4%)	175 (97.2%)	170 (94.4%)
Better	128 (71.1%)	148 (82.2)	5 (2.8%)	10 (5.6%)
Fair	6 (3.3%)	5 (2.8 %)	-	-
Poor	-	1 (0.6%)	-	-
Much poor	-	-	-	-

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Data Availability:

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

Disclosure:

This study was presented as a poster in 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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