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ORIGINALIA

SUMMARY

– Introduction: The administration by injection of hyaluronic acid (HA) for 3-5 weeks is effective in the treatment of patients with knee osteoarthritis (OA). Other products for intra-articular use have been recently introduced for the treatment of OA. Among these, a medical device, MD-Knee, produced by Guna S.p.A.; this study aims to estimate the cost-minimization of MD-Knee versus HA in the treatment of knee osteoarthritis.

– Methods and Results: We performed a cost-minimization analysis (CMA). The CMA was conducted from the perspective of the Italian National Health Service (NHS). Only direct medical costs (MD-Knee and HA) were considered. We performed a sensitivity analysis to test the robustness of the results. The mean 6-month cost per patient was € 75,00 with MD-Knee and € 185,00 with HA.

– Conclusion: From the Italian National Health Service's perspective, MD-Knee appears to be the cost-saving therapeutic option compared with HA in the treatment of patients with knee osteoarthritis.

KEY WORDS **COST, HYALURONIC ACID, ITALIAN NHS, MD-KNEE, SUPARTZ®**

A COST-MINIMISATION ANALYSIS OF MD-KNEE VERSUS HYALURONIC ACID IN THE TREATMENT OF PATIENTS WITH KNEE OSTEOARTHRITIS

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– ORIGINAL RESEARCH ARTICLE

INTRODUCTION

Osteoarthritis **(OA)** is a chronic degenerative disease of the joints that typically causes progressive damage to the articular cartilage and underlying bone (1).
It is one of the most common chronic diseases, with a prevalence of 11% and 24% in the adult population for the hip and knee OA, respectively (1).
It was estimated that approximately 303 million people worldwide were affected by OA in 2017 (2).
OA, which is more prevalent in the elderly population, is the most common cause of disability, including limitation of daily activities, and particularly pain (1). The pain is exacerbated by movement and decreases on resting, but as the disease advances, it can also occur when at rest.
The burden of disease associated with musculoskeletal diseases is continually increasing, becoming the second leading cause of disability in 2015 (years lived with disability, YLDs) (3).
Various studies have also investigated the existence of a possible relationship between OA of the knee and premature mortality.
These have identified an indicator of unfavourable results due to the limitations caused by musculoskeletal disease on the daily activities and physical functionality of the patients affected (4-8).
The FDA define the term "serious" as a disease or condition associated with morbidity that has substantial negative

impact on the day-to-day functioning of the individual (9).
OA shows all the characteristics of a serious condition. It restricts the essential daily activities of the person (walking, eating, communicating or taking care of themselves or other family members), causes premature ageing due to the loss of functionality within society, and increases the risk of mortality compared with the general population (9).
Since the life expectancy of the general population is continually increasing, the number of people with OA is also expected to grow.

– For the purpose of relieving pain and achieving an optimal clinical condition for the management of OA, International Guidelines recommend a therapeutic strategy that includes: **1)** non-pharmacological treatment (physiotherapy and rehabilitation), **2)** pharmacological treatment (non-steroidal anti-inflammatory drugs, analgesics, chondroprotective agents and intra-articular treatments), and **3)** surgical treatment (advanced stages of the disease) (10-15).

Much emphasis has been placed on non-pharmacological management over the past decade (1).
However, perhaps because the associated recommendations have not been sufficiently clear in terms of the timing, intensity, frequency, duration and implementation of procedures, various studies have shown that the non-pharmacological management of OA has not always led to optimal care results (16,17).
Although scientific evidence suggests low efficacy, paracetamol is widely recommended for the analgesic treatment of OA in the initial stages.
However, because this is associated with adverse events affecting the gastrointestinal system, cardiovascular system, liver and kidneys in the general population (especially in patients taking high dosages), its use must be carefully evaluated (18).

Among the pharmacological options, hyaluronic acid administered by infiltration plays a major role because it enables pain control and improves joint mobility, especially that of the knee (19). Double-blind controlled clinical studies have demonstrated its superior efficacy when compared with saline solution, arthrocentesis and NSAID treatments, along with an excellent tolerability profile (20,21). Hyaluronic acid has a well-known mechanism of action.
As well as safeguarding the viscoelastic properties of the synovial fluid, it plays an important part in maintaining the structural and functional characteristics of the articular cartilage (20,21).
Viscosupplementation is a procedure that involves the intra-articular infiltration of hyaluronic acid. Among the hyaluronic acid products currently available, **SUPARTZ®** is the most extensively analysed in clinical studies and the most widely used in practice (22).

– Since 2010, the treatment of painful and degenerative diseases of the musculoskeletal system has included an innovative therapeutic approach involving injectable medical devices (MD) based on porcine collagen.
Among those that are currently on the market is **MD-Knee** (Guna S.p.A.), a medical device available in vials of injectable solution based on porcine collagen. Porcine collagen is a good choice because of its biochemical similarity and the fact that porcine tissues have a very high average collagen content (19).
The reason for introducing collagen locally is structural, since the mechanical support provided by collagen constitutes an effective natural support scaffold (bio-scaffold).
This is because collagen replaces, strengthens and protects the cartilage, tendons, ligaments and joint capsules (23-26).

OBJECTIVE

The purpose of this economic assessment is to compare the benefits and costs of treatment associated with MD-Knee and SUPARTZ® in the treatment of knee OA in a hospital setting.

MATERIALS AND METHODS

Premise

The first phase of this economic assessment was based on a literature review carried out by consulting the PubMed database, to determine whether there were any clinical studies that had directly compared the two pharmacological treatment options (head-to-head).
There was only one study that satisfied this requirement (22). Its main features are summarised in the section on "clinical data".

Clinical data

The clinical study (randomised, double blind, prospective and multicentre), conducted in Italy by Martin-Martin *et* Al. assessed the non-inferiority of MD-Knee versus hyaluronic acid (SUPARTZ®) in the treatment of patients with knee OA.

– Enrolment onto the study began in March 2013 and ended in September 2013. Only patients with symptomatic OA of the knee were considered (please refer to the publication for specific inclusion and exclusion criteria). A total of 64 patients were enrolled, 32 of whom were treated with MD-Knee and 32 with SUPARTZ®. The study involved a total of 3 consultations per patient, one at the time of enrolment and a further two at 3 months and 6 months after enrolment.
The dosage regimen adopted for the two options was as follows: for MD-Knee, intra-articular injection of 4 ml collagen (two 2 ml-vials) once a week for 5 consecutive weeks; for SUPARTZ®, intra-articular injection of 2.5 ml hyaluronic acid once a week for 5 consecutive weeks.
The primary endpoint of the study was the Lequesne index of severity for osteoarthritis of the knee (ISK), while the Visual Analogue Scale (VAS) and the SF-36 questionnaire were the secondary endpoints (27). The ISK assessed the

severity of the knee OA, while the VAS and the SF-36 questionnaire assessed, respectively, variations in the pain and physical-mental state of the patients treated.
The main demographic features of the two treatment groups proved well balanced on enrolment and are described in TAB. 1.
At the time of the 3 and 6 month follow-ups, the ISK and VAS values highlighted a significant improvement in both groups compared with those measured during enrolment, with no statistically significant differences observed.
Furthermore, there was no statistically significant difference in the scores on the SF-36 questionnaire.
The results show that both pharmacological options are equally effective in relieving the symptoms of knee OA as measured 6 months after the start of treatment.

Parameters	MD-Knee (n. = 32)	SUPARTZ® (n. = 32)
Age (years ± SD)	69.41 ± 8.42	69.97 ± 9.5
Females, n. (%)	25 (86.2%)	20 (64.5%)
BMI (Kg/m^2)	27.2 ± 3.78	27.3 ± 3.56
Kellgren and Lawrence grade II, n. (%)	15 (51%)	17 (55%)
Kellgren and Lawrence grade III, n. (%)	14 (44%)	14 (44%)
ISK± SD	12.45 ± 2.63	12.6 ± 3.48
SF-36 ± SD	91.41 ± 20.01	93.07 ± 17.3
VAS ± SD	7.67 ± 1.41	7.42 ± 1.35

TAB. 1

Main demographic characteristics at enrolment (22).

Assessment technique

Given that the clinical study (22) showed no differences in efficacy, it was considered appropriate to compare MD-Knee and SUPARTZ® through a **cost-minimisation analysis (CMA)**, thus placing the emphasis on the drug costs only.

Timeframe

In accordance with the observation period of the reference clinical study (22), an analysis time period of 6 months, or 26 weeks, was adopted.

Analysis perspective

Since the two drugs are not currently reimbursed by the Italian National Health System, and the respective administrations tend to be carried out in a hospital setting (outpatient department or day hospital), the analysis perspective adopted here is that of the hospital, on the assumption that the same facility will be responsible for the purchase.

Consumption of resources and unit costs

The consumption of the two treatment regimens was calculated by multiplying the dosages indicated in the clinical study (22) by the corresponding market prices (retail price). A retail price of **€ 75.00** for a pack of ten 2 ml-vials of **MD-Knee** and a retail price of **€ 185.00** for a pack of five 2.5 ml pieces of **SUPARTZ®** were taken into account.

In accordance with the objective of the study (to estimate the incremental costs between the two therapies) and with the economic assessment technique adopted (CMA), no cost associated with administration was considered, insofar as it was assumed to be the same in both cases (weekly administration for 5 consecutive weeks).

Since no significant differences in terms of tolerability had been identified in the reference clinical study (22), no costs for the management of adverse events relating to the treatment administered were taken into account.

Sensitivity analysis

As stated in the Guidelines drawn up by the AIES group (Associazione Italiana di Economia Sanitaria) [Italian Association of Health Economics] (28), the sensitivity analysis should involve detailed analysis of the uncertainty of the result of the base case (or reference case, CDR).

In this assessment, the uncertainty analysis was carried out exclusively with reference to the purchase prices of the two pharmacological options. In this regard, to estimate the uncertainty relating to this variable, a threshold analysis was conducted in order to estimate the reductions in purchase price for which the two options would be cost-neutral.

RESULTS

Cost minimisation analysis

TAB. 2 shows the CMA results illustrating the average treatment costs for the two therapeutic alternatives.
– It is clear that, in view of the lower cost per single administration (**€ 15.00** vs **€ 37.00**), the patient treated with MD-Knee is associated with a lower average cost of treatment (**€ 75.00** vs **€ 185.00**), resulting in a saving of **€ 110.00** over the entire treatment cycle.

Sensitivity analysis

The threshold analysis conducted to estimate the uncertainty associated with the retail price shows how, if the price of MD-Knee is kept constant (base case), then only if there were a signifi-

TAB. 2

Results of the cost minimisation analysis.

Parameters	A	B
	MD-Knee	SUPARTZ®
Dose per administration	4 ml	2.5 ml
Cost per administration	€ 15.00	€ 37.00
Total No. administrations	5	5
Average cost of treatment	€ 75.00	€ 185.00
Difference (A-B)	**-€ 110.00**	

cant reduction in the price of SUPARTZ® **(-59.5%)** would the two therapeutic alternatives be cost-neutral, i.e. they would add up to the same average cost per patient treated (FIG. 1).

DISCUSSION

OA is a clinical condition that features in a large section of the population, especially the elderly. The constant and continuous ageing of the population due to the increase in life expectancy suggests that, in the near future, the number of patients affected by this disease will rise, and of these, approximately one quarter will suffer from knee osteoarthritis.

– As highlighted in other studies published in the literature, the adoption of a non-pharmacological strategy does not always prove an effective measure in countering OA (16,17).
For this reason, the identification of a pharmacological option that provides a satisfactory clinical response and, at the same time, delays or prevents surgical intervention, is becoming fundamental to addressing the problems associated with OA.
Among the pharmacological treatments, the administration of hyaluronic acid has proved to be more effective than using nonsteroidal anti-inflammatory drugs or analgesia (20,21).
The subsequent arrival on the market of injectable medical devices based on porcine collagen constituted an equally effective option in the management of knee OA, as also shown by the direct comparison study conducted in Italy by Martin-Martin *et al.* (22).

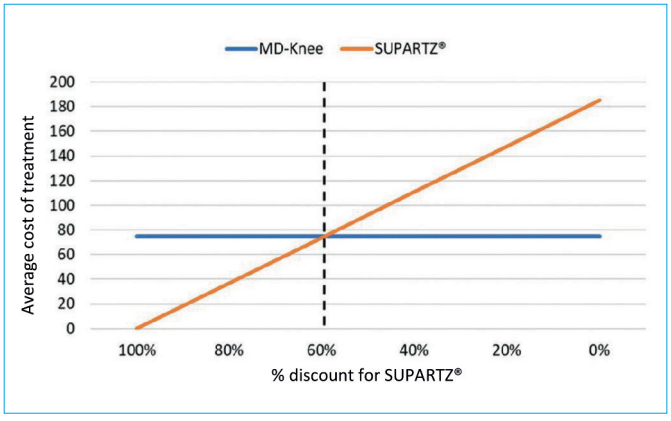
For the same effectiveness (22), the cost of treatment might be a subsequent driver of therapeutic choice, especially if considered within a broader discussion on the sustainability of healthcare spending.

In the light of the above, the intention here was to conduct a cost minimisation analysis aimed at comparing the cost associated with MD-Knee, an injectable Medical Device based on porcine collagen, with SUPARTZ®, a solution based on hyaluronic acid, over a **six-month period**.
Since neither of the drugs is reimbursed by the SSN, the hospital environment was adopted as the analytical setting, assuming that the same facility would be responsible for purchasing the drugs.
The result of the minimisation analysis showed a reduction in the average treatment cost for MD-Knee **(€ 75.00)** of **€ 110.00**, compared with SUPARTZ® **(€ 185.00)**.
Since the respective retail prices were considered, in order to take into account any discounts granted to hospitals in the event of bulk purchases of the drug, a threshold analysis was carried out to verify the price reduction for SUPARTZ® at which, if the MD-Knee were kept constant, the two alternatives would be cost-neutral.
As things stand, a reduction in the price of SUPARTZ® of almost **60%** would be required to make the average treatment cost the same for both alternatives.
It has not been done here, but it would be interesting to conduct a brief investigation to determine the average prices actually charged to hospitals for the purchase of the two drugs.
The result in favour of MD-Knee, expressed in terms of the lower average cost of treatment, could also be extended to include an analysis carried out from the point of view of the patient, thereby assuming that the patients themselves would be responsible for the drug purchase rather than the hospital.
In this case, we would be dealing with a lower impact on the social cost of knee OA.

This analysis must be read in light the of some observations.
To begin with, the comparison was carried out over a time period of just six months, as opposed to the probably longer follow-up period required for the management of knee OA.
The economic comparison actually reflects the observation timeframe adopted by the reference clinical study (22), and it was therefore considered more correct not to extrapolate the results of this to a longer time period.

FIG. 1

Threshold analysis.



A second observation concerns the fact that, in the economic assessment between the hyaluronic acid products available, only SUPARTZ® was considered.

There were two reasons for this choice: the first is that SUPARTZ® is widely used in clinical practice, with proven efficacy in previous studies, and the second is that, in the literature, there are no direct comparisons of MD-knee in relation to other types of hyaluronic acid (e.g., cross-linked, high molecular weight), which means that we cannot draw definitive conclusions on the efficacy of the MD-Knee medical device in relation to the latter.

CONCLUSIONS

Based on the results found here, it is believed that, in terms of managing knee osteoarthritis, MD-Knee constitutes a more efficient option than a medium molecular weight hyaluronic acid product such as SUPARTZ® for hospitals (or patients) since, with the same toxicity and efficacy, it leads to a lower average cost of treatment over a 6-month time period.

Disclosures

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Conflict of interest: None of the authors has financial interest related to this study to disclose.

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BULGARIAN EXPERIENCE WITH INJECTABLE COLLAGEN GUNA MEDICAL DEVICES IN SHOULDER PERIARTHRITIS

SUMMARY

This article presents two studies, whose aim was to evaluate the efficacy of collagen injections of GUNA MDs regarding pain and functional activity of the shoulder in patients with clinically proved shoulder periarthritis by Musculoskeletal ultrasound (MSUS) assessment.
We randomized 20 patients with periarthritis and subacromial subdeltoid (SASD) bursitis in Study 1, and 22 patients with periarthritis and rotator cuff (RC) partial thickness tears (PTTs) in Study 2.
Combinations of GUNA MDs were applied in the subacromial space in the total course of treatment (8 weeks), respectively GUNA MD-Shoulder + GUNA MD-Matrix in Study 1 and GUNA MD-Shoulder + GUNA MD-Muscle in Study 2.
Clinical assessment included demographic and clinical data, a Visual Analog Scale (VAS) for pain (0-100), Shoulder Function Assessment (SFA) scale (0-70) and MSUS evaluation of the shoulder. Appraisal of the efficacy according to the patient and the physician were performed.
Results of both studies showed significant efficacy on pain and improvement of SFA index. 73 to 80% of all patients had a very good and good assessment of the efficacy, which coincided with the opinion of the physician in both trials.
We proved by MSUS evaluation reduction or absence of bursitis in 80% of patients in Study 1 and complete recovery or improved structure of the RC in 77% of patients in Study 2.
No adverse events were registered.

In conclusion, collagen injections of GUNA MDs significantly reduced pain, led to a lack or decrease of bursitis volume, repaired or improved RC tissues and increased functional activity of the shoulder, thereby increasing the quality of life.

KEY WORDS

COLLAGEN INJECTIONS GUNA MDs, SHOULDER PERIARTHRITIS, SUBACROMIAL SUBDELTOID BURSITIS, PARTIAL THICKNESS TEARS, ULTRASONOGRAPHY

INTRODUCTION

About 20% of the world population have symptoms of pain and limited mobility of the shoulder (1). Shoulder pain correlates with age. Its frequency is between 6 and 11% up to 50 years of age and then increases more than twice, and ranges between 16 and 25% (2).
RC is composed of collagen, proteoglycans (PG), glycosaminoglycans (GAG), water and cells. Light microscopy shows that the primary damage is the decreasing of collagen type I, in which fibers become thinner than normal.
The extracellular matrix remodeling occurs by the impact of metalloproteinase enzymes which preceded clinical signs. Therefore, the only effective treatment would be a structural modifying treatment (3).

During the last years doctors have been looking for medical products for local injections into the joints different from the traditional medicines, such as corticosteroids. Medical products that combine positive effects on joints with no side effects.

– Treatment with injectable collagen GUNA MDs presents a concept based on the synergistic effect of non conventional and conventional medicine.
The purpose of the local administration of the collagen is essentially structural to provide mechanical support, replace, strengthen, structure and protect the zone where is injected. Due to its low dose (300 mcg), collagen acts signally, changing extracellular matrix and leading to the activation of cellular functions.
GUNA MD-Shoulder has analgesic effect on joint pain, reduces degenerative changes in the RC of the shoulder through the enhancement and strength-

ening of the collagen matrix in tendons, muscles, ligaments and joint capsule, which reduces pain. **GUNA MD-Matrix** has an antioxidant activity, improves the functions and regenerates the extracellular matrix, activating the cellular functions.
This results accelerate the healing process through faster resolution (drain effect) of swelling. **GUNA MD-Muscle** improves muscle tone by inhibiting the uptake of calcium and the enzyme phosphodiesterase (5,6).

Musculoskeletal ultrasonography **(MSUS)** is an approved imaging technique for diagnosis of RC pathology of the shoulder and monitoring of therapy (7-18). Sonographic assessment was performed according to OMERACT Group recommendations. All patients were examined with commercial, real-time equipment Mindray M5 (China) using a 7.5-10 MHz linear phased array transducer. A standard scanning protocol including multiplanar, dynamic and bilateral evaluation was followed in order to avoid missing the assessment of one or more anatomic structures of the shoulder. Transverse and longitudinal planes from the Biceps tendon **(BT)**, Subscapularis tendon **(SSC)**, Supraspinatus tendon **(SSP)**, **SASD bursa**, Infraspinatus tendon **(ISP)** and the Acromioclavicular joint **(ACJ)** were scanned.
The BT and ACJ were scanned in neutral position of the shoulder with flexed elbow at 90°.
The SSC tendon was assessed in full external rotation of the shoulder. Each patient's arm was put into full internal rotation with the hand placed posterior to the spine for the assessment of SSP tendon. The ISP tendon was assessed in shoulder adduction with the hand on the opposite shoulder. A dynamic view of the SSP tendon was obtained by moving the patient's arm from a neutral position to a 90° abduction in order to detect encroachment of the acromion into the RC. The SASD bursa lies between the RC tendons and the Deltoid muscle, overlying the Bicipital groove and it is often invisible due to the small amount of fluid within it. Bursa can be visible as a thin hypo/anechoic band with thickness up to 2 mm under normal conditions. Bursitis consists in abnormal hypo/anechoic intrabursal material that is displaceable and compressible.
RC tendons are hyperechoic due to their fibrillar echotexture. PTT is discontinuity of fibres without signs of retraction. It can be visible as an anechoic focus inside the tendon. The tendon surface retains with normal convexity. PTTs could be classified as Bursal sided, Articular sided and Intra-substance tears according to their location within the tendon (10-17).
To objectify the MSUS evaluation, two trained and experienced sonographers with at least 5 years experience in MSUS scanned together each patient and reached consensus on the US findings.

Clinical assessment included demographic and clinical data, a Visual Analog Scale (VAS) for pain (0-100) and Shoulder Function Assessment **(SFA)** scale (0-70). Evaluation of the efficacy according to the patient and the physician were performed (19,20). The SFA test has **2** items concerning pain on motion and at rest; **4** items for shoulder function in daily activities; and **3** objective Range of Motion (ROM) measures. The SFA consists of two Visual Analogue Scales (pain at rest and during movement), four multiple choice questions about daily activities (dressing, combing hair, washing opposite axilla, and using the toilet), and three measures for ROM (total active abduction and two combined movements asking the patient to place the hand on the head with the el-

TAB. 1
Study 1 – Inclusion and exclusion criteria.

	Inclusion criteria	Exclusion criteria
1	Age 18-80 years	Joint inflammatory and rheumatic auto-immune disease, infections
2	Clinical diagnosis: Shoulder periarthritis	Degenerative arthropathy, traumas, surgery in shoulder (incl. complete ruptures of the RC)
3	Duration of the symptoms up to **3 months**	Physiotherapy and topical corticosteroids application within a month before and during the monitoring
4	Pain by VAS over 25mm	Other diseases – diabetes mellitus, neurological diseases (incl. brachial plexitis, peripheral neuropathy)
5	**Bursitis of SASD bursa proven by MSUS**	Cancer, chemotherapy, radiotherapy

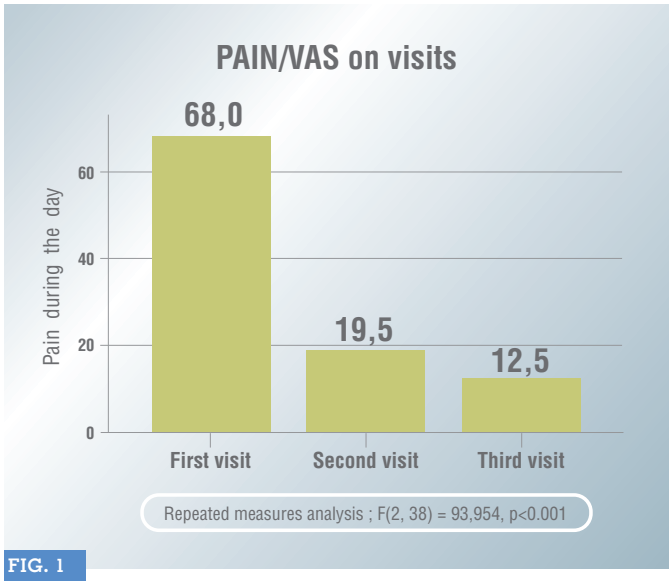


FIG. 1

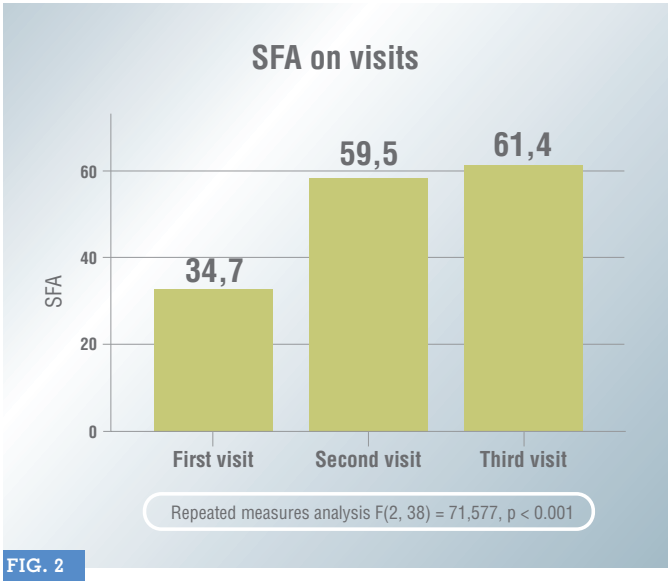


FIG. 2

bow forward and backward). The overall score ranges from 0 (worst shoulder function) to 70 (best shoulder function).

STUDY 1 – GUNA MDs EFFICACY IN SHOULDER PERIARTHRITIS WITH SUBACROMIAL SUBDELTOID (SASD) BURSITIS

The aim of this study was to evaluate the efficacy of Collagen injections of GUNA MDs regarding pain and functional activity of the shoulder in patients with **periarthritis** and **bursitis** of the **SASD**

Pain at rest	F(2, 38) = 7,914, p = 0.001
Pain during movement	F(2, 38) = 74,078, p < 0.001
Dressing	F(2, 38) = 72,724, p < 0.001
Combing hair	F(2, 38) = 63,317, p < 0.001
Washing opposite axilla	F(2, 38) = 25,294, p < 0.001
Using the toilet	F(2, 38) = 14,256, p < 0.001
Active abduction	F(2, 38) = 64,373, p < 0.001
Hand on the head with the elbow forward	F(2, 38) = 33,496, p < 0.001
Hand on the head with the elbow backward	F(2, 38) = 53,451, p < 0.001

TAB. 2
Results for each item in SFA.

FIG. 3

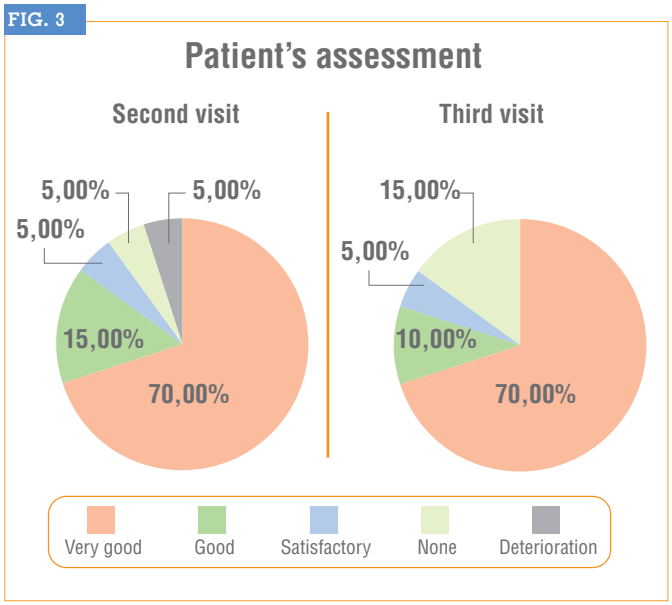
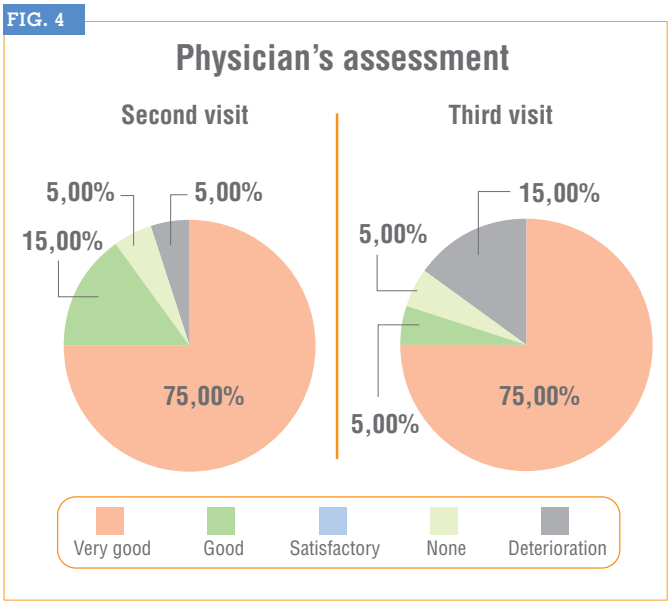


FIG. 4



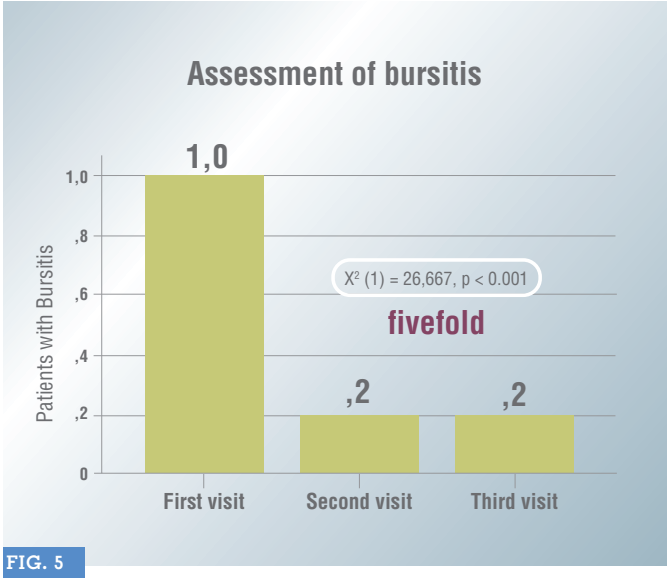


FIG. 5

bursa and duration of symptoms up to **3 months** (21-24).

MATERIALS AND METHODS

We enrolled **20 patients** with painful shoulder and proved by MSUS bursitis of the SASD bursa (TAB. 1).
At the baseline visit it was performed a standard X-Ray of the painful shoulder. Clinical assessment, VAS and SFA scale assessments (TAB. 2) were performed on the following visits: baseline (First visit), on 60th day (Second visit) and on 150th day (Third visit), as well as the evaluation of the efficacy according to the patient and the physician.
MSUS assessment was performed on all three visits (21-24).

– The combination of 1 vial of GUNA **MD-Shoulder** + 1 vial of GUNA **MD-Matrix** was applicated into the subacromial space of each patient, a total of 20 vials, 2 vials for each application, according to the scheme: first 2 weeks – 2 applications/weekly, followed by 6 weeks – 1 application/week in a general course of treatment (8 weeks) (21-24).
Collagen application technique:
The applications were performed according to generally accepted rules.
The patient's skin was sterilized with alcohol and Braunol. Access to the subacromial space was achieved with a lateral approach, inserting a 21-gauge (0.8X50 mm) needle under the anterolateral part of the acromion process, passing it through the Deltoid muscle, and directing it medially and slightly anterior to the SASD bursa, with care to avoid injection directly into the tendons of the RC (12, 24).
Statistical analysis:
For VAS and SFA assessment Repeated measures analysis was used. For assessment of Bursitis χ^2 analysis was used.

RESULTS

1. VAS Pain during the day: on the second visit (60th day) the pain during the day reduced threefold and continued to reduce till the third visit (150th day) more than 5 times compared to the first visit (FIG. 1).

2. The index of SFA had a statistically significant improvement of all SFA criteria which correlated with increasing of the point number with 24.8 points. The improvement continued till the third visit too (FIG. 2).

3. Patient Assessment: The scale had 5 levels of appraisal, from maximal (Very good) to minimal (Deterioration).
Minimum **80%** of the patients gave a very good and good assessment of efficacy of Collagen Medical Devices (FIG. 3).

4. Physician's Assessment: The scale was similar: Maximal evaluation (Very good) to minimal (Deterioration).
Physicians gave very good and good evaluation of the efficacy of GUNA MDs treatment in at least **80%** of patients on the second and third visit (FIG. 4).

5. Bursitis: MSUS evaluation showed that **80%** of patients had reduction or lack of SASD bursitis on the second and third visit (FIG. 5).
We present sonographic images in transverse scan of BT showing SASD bursa before and after the treatment with GUNA MDs. IMAGE 1 (baseline) shows the increasing quantity of fluid in the SASD bursa /hypoechoic distension of the bursa which is visible over the BT. At the second visit (after treatment) there is no sign of bursitis (IMAGE 2).

IMAGES 1-2

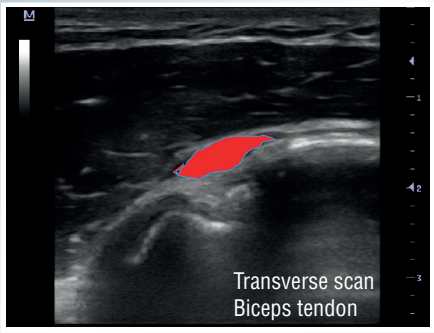


Image 1
SASD bursitis
before treatment

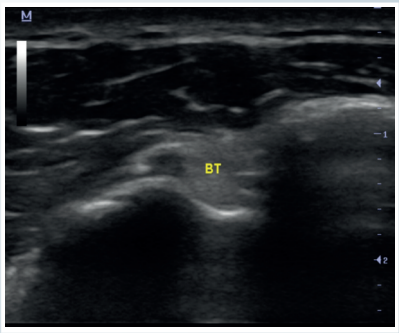


Image 2
No signs of bursitis
after treatment

STUDY 2 – GUNA MDs EFFICACY IN SHOULDER PERIARTHRITIS WITH PARTIAL THICKNESS OF THE ROTATOR CUFF TEARS OF THE SHOULDER

The aim of this study was to assess the effectiveness of the injectable collagen GUNA MDs regarding pain, functioning and recovery of periarticular tissues of the shoulder in patients with PTTs of the RC and duration of symptoms up to 7 days (25,26).
Based on cadaveric and imaging studies, the prevalence of PTTs ranges from 13% to 32%, in part related to its strong correlation to patient age. In one MRI study of asymptomatic individuals, the overall prevalence of PTTs was 20%.
In patients under the age of 40, the prevalence was approximately 4%; whereas, in patients over the age of 60, the prevalence was 26% (27-28).

Inclusion criteria	Exclusion criteria
1 Age 18-80 years	1 Joint inflammatory and rheumatic auto-immune diseases, infections
2 Clinical diagnosis: Shoulder periarthritis	2 Degenerative arthropathy, traumas, shoulder surgery. Full thickness tears of the RC
3 Duration of the symptoms up to **7 days**	3 Physiotherapy and topical corticosteroids application within a month before and during the monitoring
4 Pain by VAS over 25mm	4 Other diseases – diabetes mellitus, neurological diseases (incl. brachial plexitis, peripheral neuropathy)
5 **PTTs of the RC proven by MSUS**	5 Cancer, chemotherapy, radiotherapy

TAB. 3
Study 2 – Inclusion and exclusion criteria.

MATERIALS AND METHODS

We enrolled **22 patients** with painful shoulder and PTTs of the RC proven by MSUS.
Standard X-Ray of the painful shoulder was made at the baseline visit.
Clinical assessment, VAS and SFA scale assessments were performed on the following visits: baseline (First visit), on 30-th day (Second visit) and on 60-th day (Third visit), as well as evaluation of the efficacy according to the patient and the physician on 60-th day.
MSUS assessment was performed on the baseline and on 60-th day (25,26).

FIG. 6

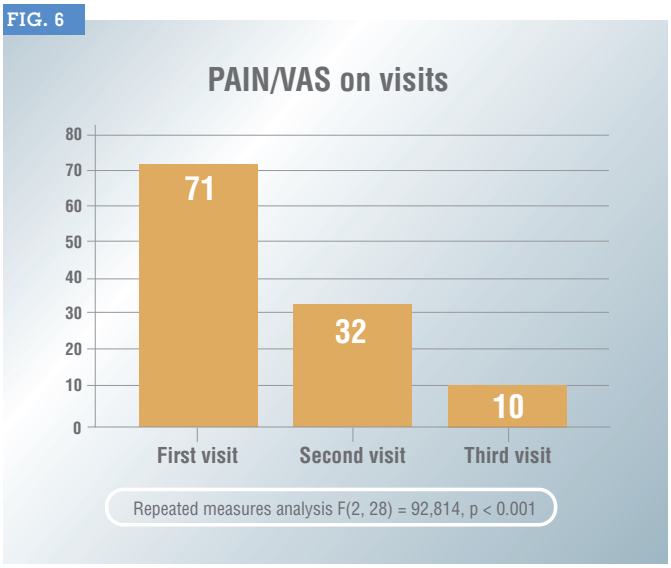
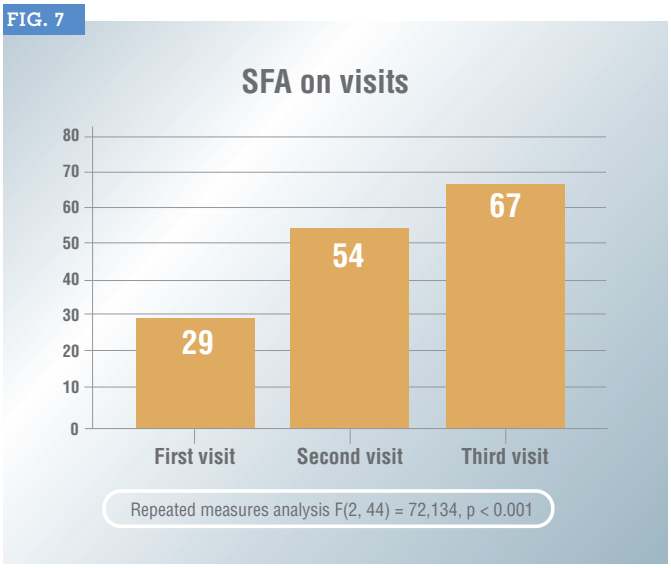


FIG. 7



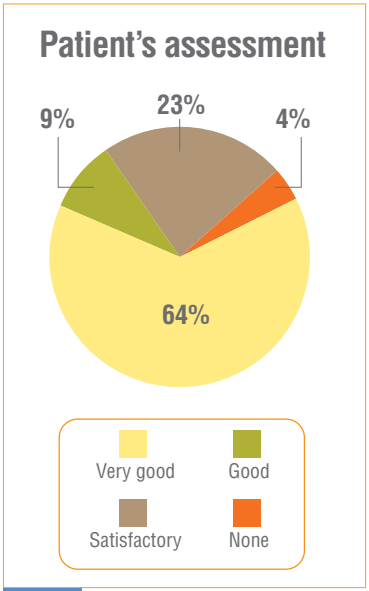


FIG. 8

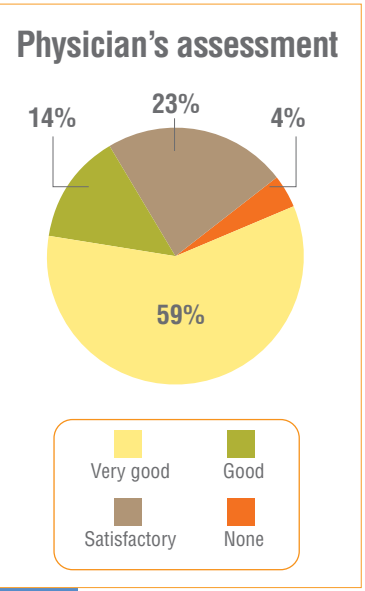


FIG. 9

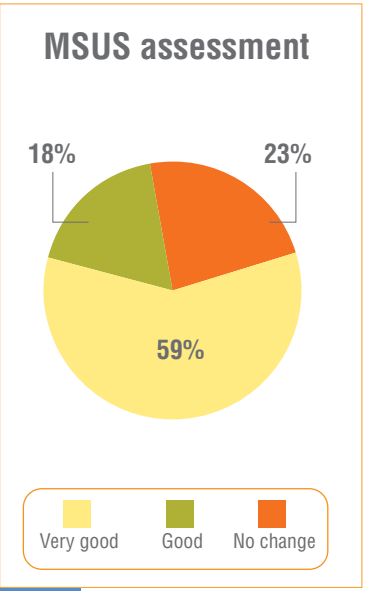


FIG. 10

– It was administered the combination of 1 vial **GUNA MD-Shoulder** + 1 vial **GUNA MD-Muscle** into the subacromial space of each patient, a total of 20 vials, 2 vials for each application, according to the scheme of Study 1, namely 2 applications weekly, for 2 weeks followed by 1 application weekly for 6 weeks (25,26).
Collagen application technique was identical to the one described above.
Statistical analysis:
For VAS and SFA assessment Repeated measures analysis was used.

RESULTS

1. VAS for Pain was significantly reduced more than twofold on the second visit and continued to reduce till the third visit, 7 times compared to the first visit (FIG. 6).

2. The SFA index had a statistically significant improvement of all criteria which correlated with an increasing of 25 points on the second visit. The improvement continued till the third visit with 38 points more compared to the first visit (FIG. 7).

3. Patient's and Physician's Assessments: **73%** of the patients gave a very good and good assessment of efficacy (FIG. 8), which coincided with the opinion of the Physician (FIG. 9).

4. MSUS evaluation: **77%** of patients had a complete or improved structure of the RC at the third visit (FIG. 10).
We present sonographic images in transverse scan of SSP tendon before treatment showing PTT presented as anechoic band (Intra-substance lesion) on the background of tendinosis (IMAGE 3) and recovered tissue of the tendon after the treatment with GUNA MDs (IMAGE 4).

IMAGES 3-4

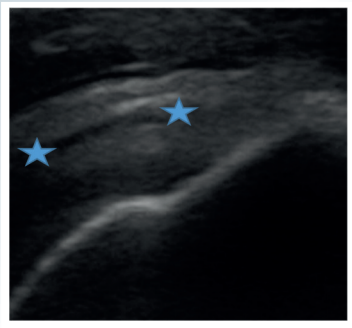


Image 3
PTT of SSP tendon
before treatment

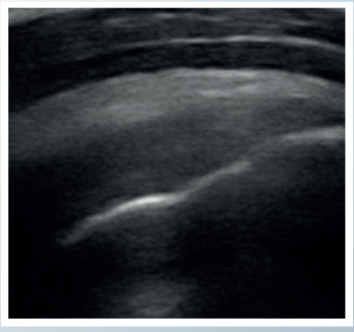


Image 4
No signs of PTT
after treatment

CONCLUSIONS

The GUNA MDs injections significantly affected pain, SASD bursitis, PTTs of the RC and functional activity of the shoulder. Efficacy assessment was high: **73** to **80%** according to the patient and the same percentage according to the physician. **80%** of patients in the **First study** were without bursitis after treatment and they had full recovering of the RC on the second and third visit.
77% of patients with PTTs in the **Second study** had full recovery or significant sonographic improvement of the fibrillar echotexture of the RC tendons.
All these data proved strengthening and restoring effect of GUNA MDs on collagen structures.

– Collagen Medical Devices GUNA in patients with Shoulder periarthritis and bursitis showed the following benefits:
1. High individual clinical response:

pain (VAS), movement (Likert), Patient's assessment

2. High objective clinical response: Tests, SFA, Sonographic assessment, Physicians's evaluation

3. Successful treatment of SASD bursitis

4. Strengthening and restoring effect on collagen structures of the RC tendons, recovery in cases of incomplete RC lesions

5. Maintenance of the result beyond the last injection

6. Increasing patient quality of life

7. Total absence of adverse side effects.

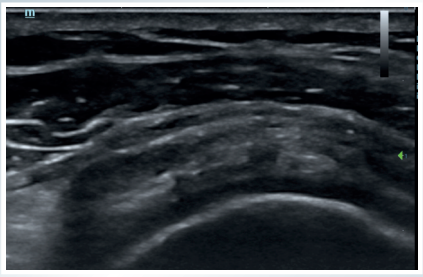


Image 5
SSP tendonosis
and not distended SASD bursa

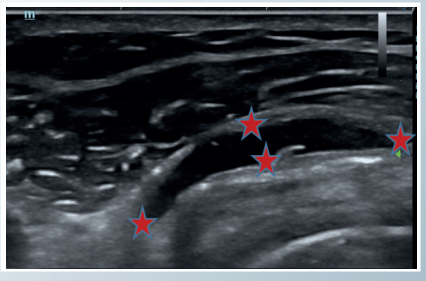


Image 6
SASD bursa is distended
by GUNA MD-Shoulder

IMAGES 5-6

GUNA MDs UNDER ULTRASOUND CONTROL IN RC PATHOLOGIES OF THE SHOULDER

In the past few years there has been an exponential growth of number of studies published in this field reflecting the growing interest to implement these technique as part of the standard clinical practice (28).

This method of drug application is safe and efficacy is higher than blind injections.

Application technique under US control is performed after skin disinfection according to generally accepted rules.

A 21-gauge (0.8X50 mm) needle penetration is "in plane" with angulation of 90°. After skin, subcutaneous tissue and Deltoid muscle penetration, the needle tip reaches the bursa. Real time injection can be rapidly carried out and drug deposition and dispersion can be checked immediately after finalizing the invasive procedure (28).

– We present some images of SSP tendinosis and GUNA MDs applications within the SASD bursa under US control:

IMAGE 5 shows SSP tendinosis and not distended SASD bursa. Tendon is thickened and hypoechoic (tendon is swollen and its typical fibrillar echotexture is lost). In this case is better to apply GUNA MD injection within the SASD bursa and – this way – to avoid the risk of tendon lesion after the needle entering into the tendon tissue.

IMAGE 6 shows distended SASD bursa by MDs Shoulder and Muscle. Note anechoic appearance of the MDs within the bursa.

In IMAGE 7 is well visible the hyperechoic profile of the needle reaching the SASD bursa and injecting MD-Shoulder and MD-Muscle.

IMAGE 7

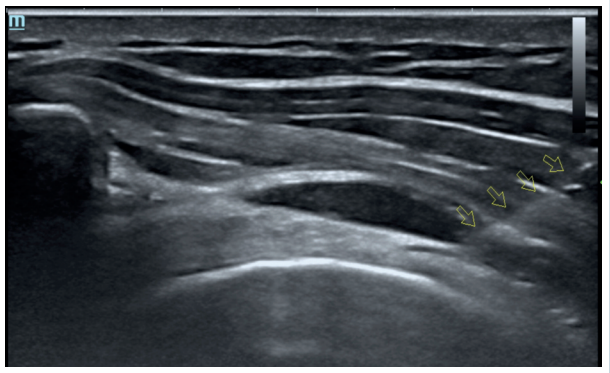


Image 7
Hyperechoic profile of the needle (arrows)
entering the bursa and filling it with MD-Shoulder and MD-Muscle

▶ In conclusion, the collagen injections of GUNA MDs are an innovative and effective approach with regenerative and analgesic effect in the treatment of Shoulder periarthritis with bursitis and/or PTTs.

Their easy application and total absence of side effects make them a modern device of choice in the physician's daily practice.

There is a new opportunity to apply GUNA MDs under US control which is a choice of the specialist. ■

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Paper presented at the 2nd INTERNATIONAL CONGRESS

"COLLAGEN IN THE PATHOLOGIES OF THE MUSCULO-SKELETAL APPARATUS - Painful diseases of Joint & Muscle System. Important contribution of Collagen Medical Devices"

Milan, 16th November 2019

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CLINICAL

D. Hernandez Herrero

VALUE OF PAIN AND SATISFACTION AFTER TREATMENT WITH SUBCUTANEOUS COLLAGEN IN PATIENTS WITH EPICONDYLITIS REFRACTORY TO OTHER TREATMENTS

SUMMARY

Epicondylitis is the most common musculoskeletal disease of the elbow. Above 20% persist beyond one year, affecting the patient's quality of life and producing significant healthcare costs. There is not a consensus about the best treatment to be applied in this pathology.
Objective: to assess the efficacy of subcutaneous collagen in the treatment of epicondylitis.
Materials and methods: a prospective study, before/after design, involving 21 patients with chronic epicondylitis refractory to other treatments and treated with local subcutaneous collagen. The pain assessment was performed using the Visual Analog pain Scale (VAS) and the functionality of the upper limb using the DASH (Disabilities of the Arm Shoulder and Hand) questionnaire and the QuickDASH (a shortened version of the DASH Outcome measure).
Results: 21 patients (12 M and 9 F), with a mean age of 47.7 years. Average time of evolution of epicondylitis 332 days. The pain went from 7.8 points on average before treatment to 2.7 points at the end, and 0.7 points after 1 year of follow-up. The DASH questionnaire score before treatment was 43 points, 19 at the end, and 14 points after 1-year follow-up.
Conclusions: Collagen, injected subcutaneously in the treatment of refractory epicondylitis, produces a statistically significant improvement in pain and functionality of the affected limb.

KEY WORDS

LATERAL EPICONDYLITIS, REFRACTORY TREATMENT, SUBCUTANEOUS INJECTION, COLLAGEN, PAIN, FUNCTIONALITY, DASH SCORE

INTRODUCTION

Epicondylitis is an enthesopathy located in the lateral epicondyle of the humerus, related with functional overload.
It is the most frequent pathology in the elbow, with a prevalence of **1-3%** in the general population.
It is related with work and sports activities (tennis elbow) that require repeated and sustained movements of wrist and fingers extensor muscles, and forearm supinator.
Specifically, the *carpal radialis brevis extensor*, the *digitorum communis extensor* and the *carpi radialis longus extensor* tend to be affected.

Epicondylitis has an important impact on work and leisure activities of patients, aggravated when the treatment is not effective, and it becomes a chronic problem.
It has been calculated that epicondylitis causes more than 200 days out of work, with direct costs up to $8000 per patient in the cases that undergo surgery, and $660 per year in those that do not require it (1).
In United States it is estimated a total cost of 22 billion dollars per year for lateral epicondylitis (2).
Although it has been considered as a self-limited process that tends to disappear in one year, recent studies argue that between 20% and 50% of patients

would have pain beyond this period of time, and this has been attributed to a process involving factors such as a central sensitization (3), local structural damage or the presence of other musculoskeletal pathologies (carpal tunnel syndrome), or previous infiltrations (4). Up to 5% of patients need surgery (5).
In the treatment of epicondylitis, multiple therapies have been used (1): stretching and muscle strengthening exercises, orthotics, thermo- and electrotherapy, iontophoresis, corticosteroids, anesthetics infiltrations, prolotherapy, platelet-rich plasma, etc. without any treatment having proved to be more effective than the others (5-7).
Local injection of collagen in the area of injury can be considered as another treatment possibility in this type of pathologies for which its commercialization is authorized, although the absence of published studies can make question about its effectiveness.
The possibilities of using purified collagen, locally injected, for the treatment of tendon and ligament pathologies, is based on studies that demonstrate the ability of fibroblasts to answer to physical stimuli adapting themselves to the structural characteristics of extracellular environment. These cells are capable of undergoing a process of polarization of their cytoskeleton to confer tissues their characteristics of tensegrity, resistance and elasticity (8). The degenerative pathology of support structures is related to the loss of these characteristics at microstructural level (9).

MATERIALS AND METHODS

Twenty-one patients were diagnosed with epicondylitis and treated as outpatients.
A quasi-experimental prospective follow-up study, designed as before-after intervention, was carried out for a year with the objective of controlling the results in terms of pain and functionality (FIG. 1).
All of them had previously received conservative treatment (stretching, electrotherapy, ultrasound, laser, shock wave therapy -SWT) or infiltrations without favorable clinical results. In the cases treated with SWT or infiltrations a washing period of 3 months was left.

– All patients were treated with **Guna MD-Shoulder**, marketed in 2 ml vials of product consisting of 99% purified porcine type 1 collagen and 1% Iris versicolor extract.

– The treatment consists in subcutaneous injections of 10 vials of 2 ml of MD-Shoulder. The procedure was always the same: once the epicondyle was located, 4 points around it were infiltrated, creating a 0.5 ml subcutaneous blister, on which pressure was subsequently made until disappeared.
The first four injections were made 2/week, and the remaining six 1/week. The complete treatment lasted 8 weeks.
All patients signed informed consent before starting the treatment.

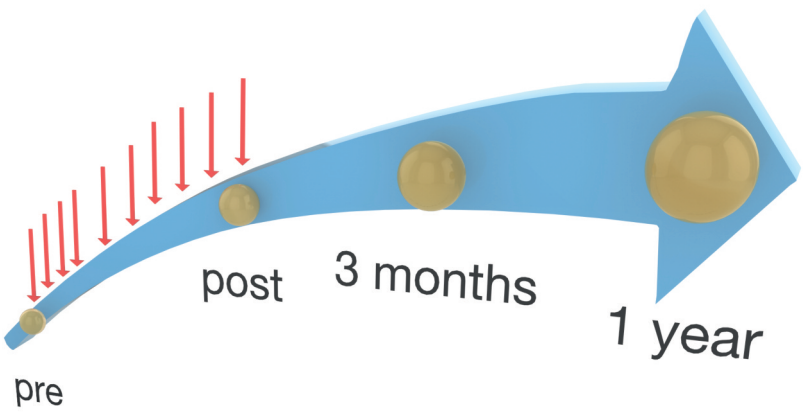

FIG. 1
Protocol.

At the beginning of the treatment, all patients were instructed to perform daily stretching exercises of the antebrachial muscles at home. After completion, eccentric enhancement exercises were added. To facilitate the performance of the exercises, patients received a copy of them obtained from the exercise program of the *Sociedad Española de Rehabilitación y Medicina Física* (SERMEF), available on the society's website (http://www.sermef-ejercicios.org).
During the treatment, no limitation was established regarding work or sports activity performed by the patients.
Pain assessment was performed using the Visual Analog pain Scale **(VAS)** score 0-10.
The evaluation of functionality of the upper limb was carried out using the self-administered questionnaire DASH *(Disabilities of the Arm Shoulder and Hand)*, adapted to Spanish, and the QuickDASH, which is a 11-item reduced version of the same questionnaire, which has demonstrated an adequate correlation of results.

– These evaluations were made **at the beginning** of the treatment, **at the end**, **at 3 and 6 months** and **at one-year follow-up**.
In this last consultation, the QuickDASH questionnaire was used in 10 of the 21 patients by telephone.

The score of the results of the DASH and the QuickDASH questionnaires was carried out using the online available tool on the official website of the questionnaire (http://www.dash.iwh.on.ca/).
The DASH questionnaire is a self-administered scale, adapted to spanish.
It consists of 30 items and two optional modules of 4 items each, which are scored from 1 to 5.
The two optional modules refer to the individual's work and leisure activities and are scored following the same scheme. The final score can be from 30 to 150 points, which is subsequently transformed into a scale of 0 to 100, where 0 is the best possible score and 100 the worst.

Patient	Age	Gender	Affected Side	Laterality	Evolution Time (Days)	Profession
1	44	F	Right	Right-handed	365	Office worker
2	34	F	Right	Right-handed	480	Saleswoman
3	55	F	Left	Right-handed	90	Cleaner
4	46	M	Right	Right-handed	180	Policeman
5	47	M	Right	Right-handed	120	Farmer
6	39	M	Left	Right-handed	548	Technician
7	45	M	Right	Right-handed	365	Technician
8	51	M	Left	Left-handed	182	Graphic designer
9	48	M	Right	Right-handed	365	IT specialist
10	72	M	Right	Right-handed	90	Retired
11	40	M	Left	Right-handed	548	Welder
12	33	F	Left	Right-handed	730	Cleaner
13	45	M	Right	Right-handed	735	Graphic designer
14	51	F	Right	Right-handed	365	Cleaner
15	45	F	Left	Right-handed	90	Clinical assistant
16	64	F	Right	Right-handed	180	Housewife
17	64	F	Right	Right-handed	240	Office worker
18	34	F	Right	Right-handed	180	Physiotherapist
19	47	M	Left	Right-handed	365	Jeweller
20	51	M	Left	Right-handed	400	Watchman
21	48	M	Right	Right-handed	365	Policeman

TAB. 1
Patients characteristics.

For the scale to be valuable, patients must have answered at least 27 of the questions in the main questionnaire and 4 questions in the optional modules.
On the same webpage there is a similar tool for scoring the QuickDASH questionnaire, although in this one, being only 11 questions, 100% of them must have been answered.

– The study was conducted between September 2014 and November 2016, when the last patient finished the one-year follow up period.
In May 2017, 18 patients were contacted by phone to know their evolution over time, measuring pain with a 0-10 points phone-administered question, and asking for satisfaction with treatment with a 5 points Likert scale.
The computerized management of the data and the statistical study was carried out using the MS Excel 2007®.
For the statistical study, the comparison of the results of the assessment scales at the different cut-off points was performed using the Student t test for paired data, establishing a statistical significance $p < 0.05$.

RESULTS

TAB. 1 illustrates the demographic and work characteristics of the 21 patients: 12 M and 9 F, with an average age of 47.7 years. They refer pain in epicondyle for a mean of 332 days of evolution (range 90-735 days). 20 of the patients were right-handed and 1 left-handed. In the case of the left-handed patient, the affected side was dominant. Among right-handed patients, 13 have the dominant side affected and 7 the non-dominant side.
TAB. 2 illustrates the results obtained in the measurements of pain and function-

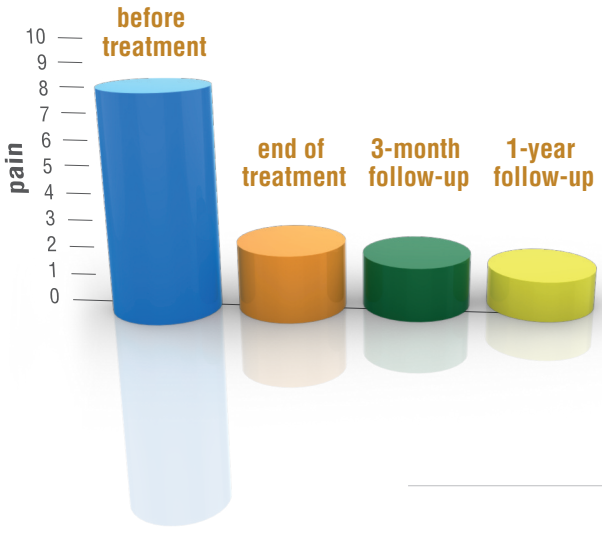

FIG. 2
VAS evolution.

Patient	BEFORE TREATMENT				END OF TREATMENT				3 MONTHS OF MONITORING				1 YEAR FOLLOW-UP			
	DASH	LEISURE DASH	LABOR DASH	VAS	DASH	LEISURE DASH	LABOR DASH	VAS	DASH	LEISURE DASH	LABOR DASH	VAS	DASH	LEISURE DASH	LABOR DASH	VAS
1	57.5	75	75	7	26.7	75	50	3	15.5	75	25	0	2.5	NV	6.3	0
2	56.7	68.8	50	7	50.9	NC	50	6	NV	NV	NV	5	36.4	NV	12.5	0
3	NV	NC	75	6	12	NC	12.5	0	NV	NV	56.3	5	50	NV	25	0
4	43.3	56.3	56.3	8	9.2	50	25	2	30.8	50	50	0	0	2.5	0	0
5	36.1	NC	50	7	54.3	68.8	100	7	NV	NV	NV	0	0	NV	0	0
6	16.7	25	12.5	9	9.2	6.3	0	3	31.7	25	50	7	29.5	NV	0	5
7	37.9	NC	56.3	8	15.8	0	12.5	0	14.2	0	0	NC	0	0	0	0
8	58.3	NC	75	9	2.6	0	12.5	0	NV	NV	NV	2	11.4	NV	NV	2
9	21.6	50	50	6	18.3	37.5	25	4	NV	NV	NV	3	2.3	0	6.3	1
10	NV	NC	NC	9	7.5	NC	NC	0	1.9	NV	NV	1	0	0	0	0
11	51.7	NC	68.8	9	31.7	NC	43.8	3	27.5	NV	25	3	22.7	NV	25	0
12	35	75	50	7	7.1	NC	12.5	1	NV	NV	NV	10	9.1	NV	12.5	1
13	54.3	100	75	7	27.6	NC	37.5	2	NV	NV	NV	3	31.8	NV	NV	2
14	45.4	50	NC	7	NV	NV	NV	0	NV	NV	NV	0	0	NV	0	0
15	NV	NV	NV	8	NV	NV	NV	NC	NV	NV	NV	NC	2.3	0	0	0
16	50	NC	56.3	8	NV	NC	NV	NC	13	NV	NV	1	6	NV	18.2	2
17	29.6	NC	0	7	7.8	NC	6.3	1	8	NV	18.8	0	9.1	NV	NV	0
18	25.8	NC	81.3	10	9.2	NC	43.8	7	2.5	NV	6.3	1	4,5	NV	12.5	0
19	59.5	NC	75	8	22.3	NC	NC	8	53.7	75	100	0	45.5	NV	NV	0
20	31.7	NC	50	8	15.8	NC	31.3	1	4.2	NV	0	0	5	NV	6.3	0
21	62.5	75	75	8	14.2	25	25	4	NV	NV	NV	NC	0	NV	0	0
Mean	42.97	63.9	57.30	7.76	19.01	32.82	30.48	2.73	18.45	45	33.14	2.27	13.34	0.5	6.65	0.61
SD	14.21	21.37	21.89	1.04	14.58	30.02	24.35	2.64	15.96	32.59	31.32	2.86	16.18	1.11	8.68	1.24
Median	44.35	68.8	56.3	8	15	31.25	25	2	14.2	50	25	1	5	0	3.15	0
Rank	62.5-21.6	100-50	81.3-50	10-6	54.3-2.6	75-25	100-6.3	7-1	53.7-2.5	75-0	56.3-0	10-0	50-0	2.5-0	25-0	5-0

NC = questionnaire not answered ; NV = questionnaire not valued ; SD = standard deviation.

TAB. 2

DASH, Leisure DASH, Labor DASH, and VAS values.

ality throughout follow-up. When patient has more than 3 unanswered questions, or all of them in the optional modules are non-answered, questionnaire cannot be scored.

In two patients (#12 and #19), clinical improvement at one-year follow up was not maintained and other infiltration techniques had been used.

– Pain went from **7.8** points on average before treatment to **2.7** points at the end of it, to **0.7** points at one-year follow up (FIG. 2).

The score of the DASH questionnaire before treatment was **43** points. It decreased to **19** points at the end of it and remained at **18** points at 3 months.

It went down to **14** points at one-year follow-up (FIG. 3).

Regarding to the optional modules of the DASH, only the results of the work activity questionnaire are shown, since those of leisure and sport activities present a very low number of evaluable answers.

Again, the evolution varies from **57** points at the beginning of treatment, to **30** points at the end, **33** points at 3 months and **6.6** points at one-year follow-up.

The improvement in pain assessment at the end of the treatment was statistically significant. This improvement is maintained at one-year follow-up.

Likewise, when assessing the functionality at the end of the treatment and after one year of follow-up, a statistically significant improvement is also obtained.

– When contacted in May 2017, only one of the 18 patients refened an increase in pain. The other 17 patients have continued improving in pain measured with VAS with a mean of 1.2/10.

Despite satisfaction with treatment in a 5 points Likert scale, **17 over 18 patients** are satisfied or very satisfied with the outcomes obtained.

DISCUSSION

Epicondylitis is a relatively frequent pathology. It is related to overloads in the extensor musculature of forearm, especially involving *carpal radialis extensor* and *common extensor* of the fingers. It has been possible to establish a relationship with situations of overload at work and especially racket sport (10-11). Approximately 88% of patients recovered within a year, but there are a number of cases refractory to treatment, with persisting clinic for years, and severe impairment in functionality even at work level (12).

Different studies show that the inflammatory component of the process is less important than it might seem, and actually it is considered more a degenerative process, having to talk more about tendinosis, with disruption of fibrillar and cellular structure, and immature and anomalous repair processes (12). The main characteristics of tendinosis are abnormalities in cellularity, vascularization and collagen structure (5).

Immature cells tend to make type 3 collagen instead of type 1, altering its correct structure, with loss of cross-linking, and formation of different sizes and diameters fibers (13).

During exercise and in the resolution processes of tendon lesions, mechanical load signals initiate an intracellular cascade of genetic expression that leads to the transcription and translation of extracellular matrix proteins.

It is known that transmission of forces along the tendon depends on the structural integrity, the relationship between the individual fibers and extracellular matrix, as well as the intra and intermolecular cross-linking, the length, orientation and density of the collagen fibers (14).

Although multiple possible epicondylitis treatments have been described, it has not been possible to establish the superiority of any of them.

The most conservative treatments or even "do nothing" are recommended as the first line (1).

Exercise patterns have been described, with stretching and eccentric exercises (15), demonstrating that they are more effective than placebo or than concentric exercises (3). They are based on the need of an appropriate load for the lesion repair, and have demonstrate their effectiveness in several studies, especially with the combination of stretching and strengthening exercises, preferably eccentric and/or isometric associated (12,16,17). These exercise guidelines are more effective if they are included in a multimodal treatment program (1,18). The effectiveness of the exercises in outpatient treatment has also been evaluated, with improvement in pain and functionality (19).

The use of different thermo- and electrotherapy guidelines has been proposed, with disparate results, being described, according to different authors, is giving better results with ultrasound, laser therapy and/or ultrasonophoresis (20,21). The use of orthoses along with exercises has also been recommended but their usefulness could not be demonstrated (22).

SWT is another used technique, observing, in a systematic review (23), some favourable evidence against other therapies, including placebo or corticosteroid infiltration (12,24).

Finally, numerous papers with invasive techniques such as injections of corticosteroid, botulinum toxin (25), prolotherapy, hyaluronic acid, autologous blood and platelet-rich plasma has been published. There are multiple clinical trials, systematic reviews and meta-analysis analyzing the results with these treatments. In all of them diverse results are obtained, barely conclusive.

The latest studies place infiltrations with autologous blood preparations, platelet-rich plasma and tendon stem cells, as the most promising treatments in refractory epicondylitis (13). The latter is included in the so-called cell regenerative therapy, which consists in the injection of fibroblasts or tenocytes, with the idea of restoring the tissue's ability to regenerate extracellular matrix and repair tissue damage, favoring the synthesis of collagen in the area of injury (12).

– The use of collagen to treat supportive tissues pathologies is based on the relationship established between the alteration of the extracellular matrix and the function of the tenocytes. 60% of the tendon is made up of collagen, mostly type 1. The three-dimensional connection of the tendon fibroblasts with the surrounding collagen fibers, and the architecture of the cells themselves are the basis of a cellular interaction that sustains tension in the support tissues.

In the process of healing tendon injuries, previously resting tenocytes are activated to produce type 1 collagen by mechanoreceptors-mediated stimuli.

It has been shown that, through the transmembrane integrins, a connection is established between cytoskeleton and the fibrillar structure of the extracellular matrix, so that tensile forces trigger in-

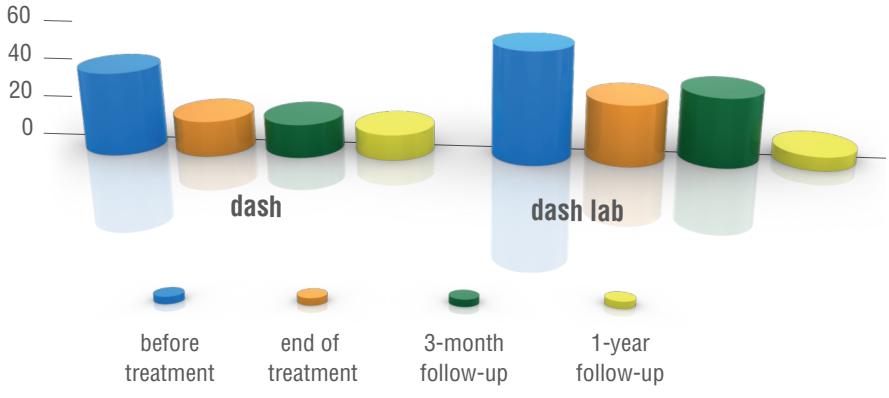

FIG. 3

DASH questionnaire.

tracellular reactions for the production of collagen proteins that are secreted into the extracellular liquid, becoming part of matrix and exoskeleton (14). Molecules such as platelet-derived growth factor or transforming-beta growth factor are involved in the regulation of the expression of type 1 collagen by fibroblasts (12). In fact, a certain mechanical stress load, as opposed to immobilization, is essential for the integrity and strength of the tendon.

– The contribution of local collagen would mean an improvement in the structure of collagen and, secondarily, by interacting with transmembrane integrins, it would stimulate an intracellular reaction that would lead to the synthesis of new collagen for the definitive repair of the injury (9).
One study has shown the efficacy of collagen in the treatment of knee osteoarthritis (26). We have not found published works on the use of injected collagen for the treatment of chronic epicondylitis, except for cases mentioned in Folch *et* Al. on chronic pain (27), in which 4% of patients suffered from epicondylitis. This study does not specify whether patients had received treatments prior to collagen infiltration and, in addition to this, 2cc of local lidocaine were infiltrated. These differences must be considered with our study, in which epicondylitis had been refractory to other usual treatments and only collagen has been infiltrated.

– Smith-Forbes *et* Al. (28) describe that to be considered as significant, the improvement in DASH must be at least 15.8 points. In our study the improvement reaches 24 points on average at the end of treatment and 29 points after one-year follow-up.
In a previous study conducted in our center (21) different types of electro- and thermotherapy were analyzed in the treatment of epicondylitis. An improvement of 15 points was obtained in the DASH questionnaire, without being able to establish what type of those treatment was more effective.
Different studies demonstrate the effectiveness of the exercises for the improvement of epicondylitis. This improvement is greater for exercises performed in a treatment center than for those performed at home. Our patients were instructed for the daily performance of eccentric stretching and strengthening exercises at home.
This could have contributed to the improvement of pain at least partially, but we consider that it would not explain the results obtained by itself, as seen in the study from Peterson *et* Al. (3).
There authors, comparing eccentric and concentric exercises, obtained a reduction in DASH from 19 points for the eccentric exercise group and 17 points for concentric exercises after one-year follow up.
Regarding pain, Fathy (6), comparing iontophoresis against Cyriax type exercises, refers decrease in pain measured with VAS at 3 months after treatment, from 6.8 to 3.2 in the iontophoresis group, and to 3.3 in the exercise group.
Manias and Stasinopoulos (29) comparing exercises with or without ice application, find pain improvement of 6.9 and 7.1 points on the VAS at 4 months respectively.
Vulpiani *et* Al. (30) achieve, after one-year follow-up, an improvement in VAS with SWT of 4.2 points and with cryoultrasonotherapy of 1.9 points. In our patients, the reduction in pain on the VAS scale at one-year follow-up is 6.9 points.
– Regarding safety and tolerability of the treatment, there have been no cases of adverse events or side effects, and it has been well tolerated by the patients, despite being a treatment that requires repeated infiltrations.

Limitations of the study

- This is a prospective follow-up of cases, without controls or randomization process.
- It may be considered that administer QuickDASH questionnaire by telephone is a relative limitation, since it is designed to be self-administered.

As a curiosity, we would like to point out the poor response that we have obtained in the DASH scale of leisure and sport, which has led us to not be able to perform an analysis of the results.
This seems strange in a pathology known as “tennis elbow”.

CONCLUSIONS

Subcutaneously injected MD-Shoulder for the treatment of refractory epicondylitis, associated with stretching and eccentric strengthening exercises, is a simple, well-accepted treatment, minimally invasive and that produces statistically significant results in long-term evolution in terms of pain and functionality, similar or superior to those that can be found in the literature with other treatment techniques.

– MD-Shoulder could thus become an option in the existing therapeutic arsenal in the treatment of refractory epicondylitis.
They are necessary randomized clinical trials to check these results and to make comparisons with other standard treatments.

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INITIAL ASSESSMENT OF EFFECTIVENESS OF INTRA-ARTICULAR MD-KNEE INJECTION THERAPY IN TREATMENT OF PRIMARY KNEE OSTEOARTHRITIS IN BACH MAI HOSPITAL - HANOI, VIETNAM

SUMMARY

Objective: Evaluate the effectiveness and side effects of intra-articular MD-knee injection therapy in the treatment of primary knee osteoarthritis.

Objects and methods: Prospective randomized longitudinal clinical trial on 60 patients with primary knee osteoarthritis, diagnosed by ACR-1991 criteria. The first group of 30 patients was treated with intraarticular injections two vials (4 mL) of MD-Knee/time/week x 5 consecutive weeks. The second group of 30 patients, treated with intraarticular injection one vial (2,5 mL) of GO-ON/time/week x 5 consecutive weeks. The two groups were assessed by using VAS, measure of knee motion angle, Lequesne scale, WOMAC, recording the side effects before (T0) and after treatment T2 (2 weeks), T4 (4 weeks), T8 (8 weeks), T12 (12 weeks).

Results: The effectiveness of pain improvement and motor function of MD Knee group on VAS, Lequesne and WOMAC scales was noticeable 4 weeks after injection and continued for up to 12 weeks.

The difference was not statistically significant compared to the group using GO-ON (p> 0.05). The best treatment effect is after 3 months: The 30% improvement rate on VAS scale is 86.7%. The average VAS score decreased by 85.2%. The 50% improvement rate on WOMAC scale is 86.7%. The overall WOMAC score averages decreased by 81.2%. The average Lequesne score decreased by 91.1%. The percentage of obvious improvement in knee range of movement is 43.3%.

The only side effect was: local tension (13.3%). The percentage of patients who were very satisfied and satisfied with the treatment was 93.3%.

Conclusions: Intra-articular MD-Knee injection therapy relieves pain and improves motor function in the treatment of primary osteoarthritis.

KEY WORDS

PRIMARY KNEE OSTEOARTHRITIS, COLLAGEN THERAPY, INTRAARTICULAR INJECTION, MD-KNEE, SODIUM HYALURONATE

INTRODUCTION

According to the WHO in 2013, osteoarthritis accounted for 10-15% of the population over 60 years of age, causing disability for 10 million women and 6.5 million men each year (1).

In Vietnam, the rate of knee osteoarthritis accounted for 56.5% of all osteoarthritis patients hospilalized in Bach Mai Hospital - Hanoi, Vietnam (2).

However, current treatments have many limitations and have not completely controlled knee osteoarthritis.

Since 2010 collagen injection therapy has been used in the treatment of degenerative diseases of the musculoskeletal Apparatus.

Reshkova *et* Al. (3), Nestorova *et* Al. (4) and Boshnakov (5) demonstrate that MD-Knee intra-articular injection therapy combined with MD-Muscle periarticular injection in the treatment of osteoarthritis has analgesic effect, improve the patient's motor function and quality of life.

In 2016, Martin-Martin *et* Al. demonstrated similar efficacy of MD-Knee and sodium hyaluronate (HA) intra-articular injection therapy in patients with knee osteoarthritis (6).

– In Vietnam, there has been no research on the effectiveness of using collagen in the treatment of primary knee osteoarthritis. Therefore, we conducted this study to evaluate the effects of intra-

TAB. 1

30% improvement rate of VAS compared to T0.

Time	T2 n	T2 %	T4 n	T4 %	T8 n	T8 %	T12 n	T12 %	p
MD-Knee group (n=30)	5	16.7	14	46.7	19	63.3	26	86.7	>0.05
GO-ON group (n=30)	7	23.3	12	40	21	70	25	83.3	
p*	>0.05		>0.05		>0.05		>0.05		

p (MD-Knee vs GO-ON). p* (T2, T4, T8, T12 vs T0).

articular **MD-Knee** injection in the treatment of primary knee osteoarthritis at the Rheumatology Department of Bach Mai Hospital - Hanoi, Vietnam.

PATIENTS AND METHODS OF THE STUDY

Patients

60 patients with primary knee osteoarthritis, diagnosed according to ACR 1991 criteria, treated in the Rheumatology Department of Bach Mai Hospital, from October 2018 to October 2019.

Patients had VAS score of 4 cm or higher, at stages 2 and 3 according to the Kellgren and Lawrence classifications, without synovial effusion. Exclusion criteria: bacterial infection, severe chronic disease, taking NSAIDs in the last 7 days or intraarticular corticosteroid injection in the last month, HA injection in the last 6 months.

– The patients were divided into 2 groups. The group, consisting of **30** patients who were injected with MD-Knee intra-articularly 4ml/time/week for 5 consecutive weeks, each injection 1 week apart.

The control group consisted of **30** patients who were injected with hyaluronic acid (GO-ON) intra-articularly injection with 2.5 ml/time/week for 5 consecutive weeks, 1 week apart.

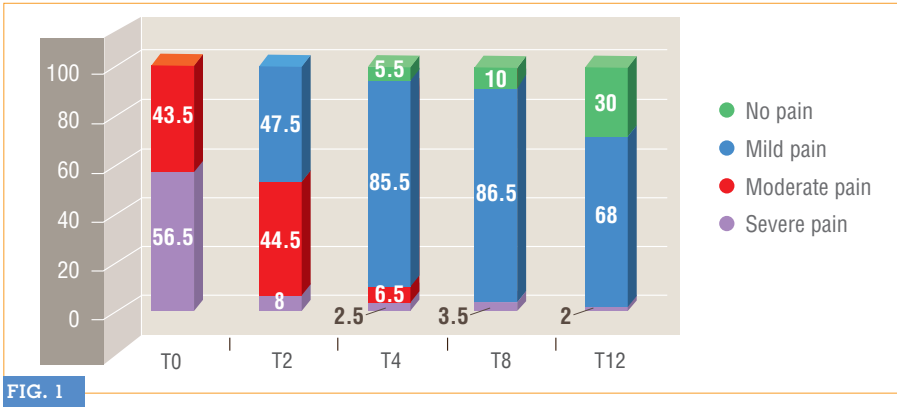


FIG. 1

VAS scale in MD-Knee group.

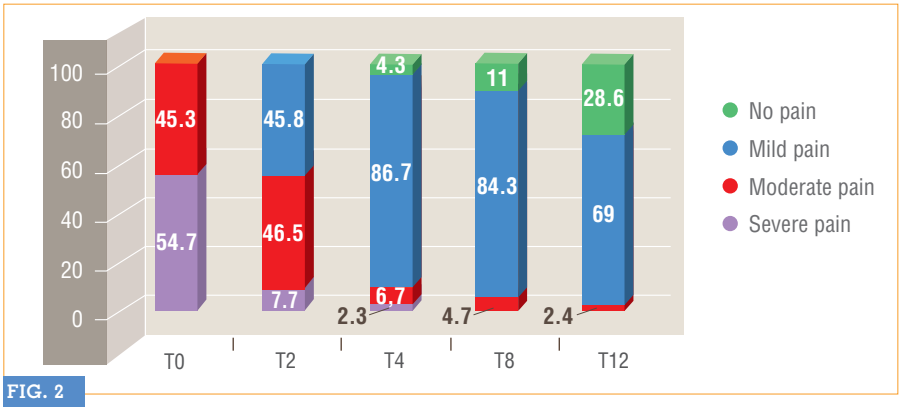


FIG. 2

VAS scale in GO-ON group.

Methods

Prospective, randomized, longitudinal clinical trial. It was assessed/measured: VAS index, measure of knee movement angle, Lequesne scale, WOMAC, sides effects before **(T0)** and after treatment at 2 weeks **(T2)**, 4 weeks **(T4)**, 8 weeks **(T8)** and 12 weeks **(T12)**.

Analysis and data processing was made using by SPSS 20.0 statistical software.

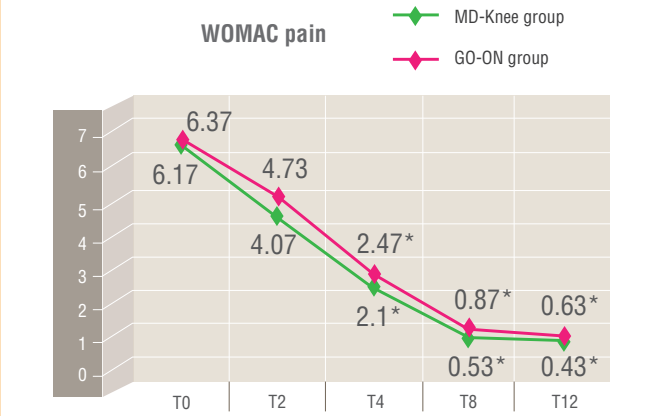
RESULTS

Demographic characteristics of the patients

MD-Knee patients had an average age of 59.07 ± 10.9, 53.3% in the age group 40-59, F 86.7%, manual workers 56.7 %, obesity rate 63.3%.

The average duration of osteoarthritis in MD-Knee group was 5.8 ± 5.5 years, the prevalence rate from 1-5 years was 36.7%.

– There was no difference in age, gender, occupation and body mass index (BMI) between MD-Knee and GO-ON ($p > 0.05$).



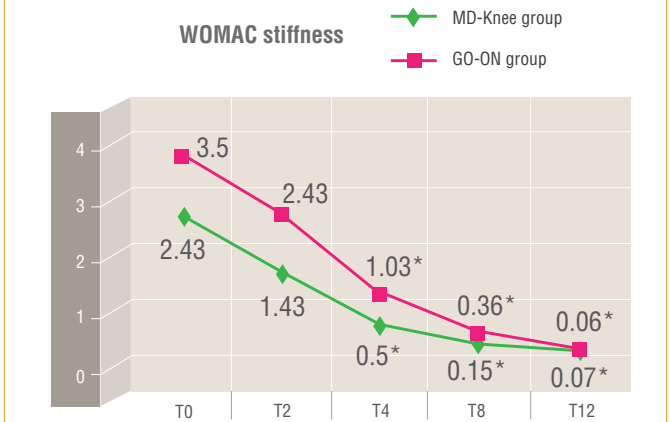


FIG. 3

Results of treatment under WOMAC pain and WOMAC stiffness of MD-Knee and GO-ON groups. p (T2, T4, T8, T12 vs T0). *: p < 0,05.

Result of treatment of MD-Knee intra articular injection therapy

– Results of treatment on a VAS scale

The MD-Knee group got an improved 30%; after 2 weeks the VAS score was 16.7% and after 12 weeks 86.7%; this improvement was statistically non significant compared to the GO-ON group (p > 0.05). There has not been a correlation between demographic factors and clinical symptoms to the rate of improvement 30% of the VAS score at the time of 12 weeks after treatment (p > 0.05). The improvement of the average VAS score of the patients with stages 2 and 3 knee osteoarthritis on X-ray all began to make sense from week 2, and continued in the subsequent weeks. The difference is not statistically significant between the 2 phases (p > 0.05). The incidence of severe pain and moderate pain in the MD-Knee group at the time T0 respectively 56.5% and 43.5%, after 2 weeks down to 8% and 44.5%, dropped to 0% and 2% in week 12. There are no statistically significant differences with the GO-ON group (p > 0.05) (TAB. 1; FIGG. 1, 2).

– Results of treatment on a WOMAC scale

The average general WOMAC point at T0 was 32.87 ± 3.19 to the time T12 was reduced to 5.20 ± 4.48 (reduced 81.2%). Symptoms of pain, stiffness, movement on the WOMAC scale begin to decline from T4 extending to T12. The difference between the times T4, T8, T12 versus T0 is statistically significant (p < 0.05). The rate of severe and moderate pain level in MD-Knee group at time T0 were 56.5% and 43.5%, after 2 weeks, it was reduced to 8% and 44.5%, to 0% and 2 % at 12 weeks. There was no statistically significant difference compared to the GO-ON group (p > 0.05). In both the MD-Knee and GO-ON groups, the improvement of the WOMAC pain and stiffness became important from the 4th week after treatment and extended to the 12th week (p < 0.05). There are no statistically significant differences between the 2 groups (p > 0.05). In 2 subgroups with stage 2, 3 Kellgren and Lawrence classification of patients with MD-Knee and GO-ON, WOMAC scale (pain, stiffness, joint mobility and WOMAC total) began to improve markedly from the 4th week, lasting until the 12th week. The improvement of 50% of WOMAC general score at times was the same between 2 Xray stages and between 2 treatment groups (p > 0.05) (TAB. 2; FIGG. 3, 4).

Time	T2		T4		T8		T12		p
	MD-Knee	GO-ON	MD-Knee	GO-ON	MD-Knee	GO-ON	MD-Knee	GO-ON	
2nd stage	4/19	8/23	8/19	11/23	14/19	18/23	17/19	20/23	>0,05
	21.0%	34.7%	42.1%	47.8%	73.6%	78.2%	89.4%	86.9%	
3rd stage	2/11	2/7	5/11	3/7	8/11	5/7	9/11	5/7	
	18.1%	28.5%	45.4%	42.8%	72.7%	71.4%	81.8%	71.4%	
p*	>0.05		>0.05		>0.05		>0.05		

p (2nd stage vs 3rd stage). p* (T2, T4, T8, T12 vs T0).

TAB. 2

Rate of improvement 50% of general WOMAC in diferents Xray stages of MD-Knee and GO-ON groups.

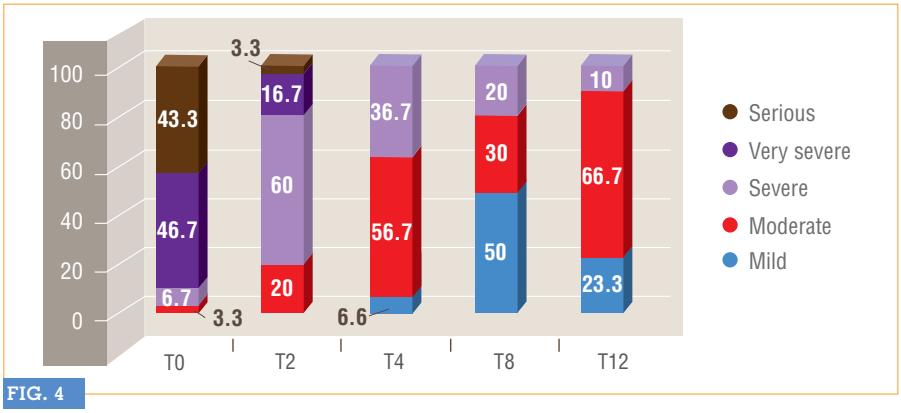


FIG. 4

Degree of knee joint damage on the Lequesne scale in MD-Knee group.

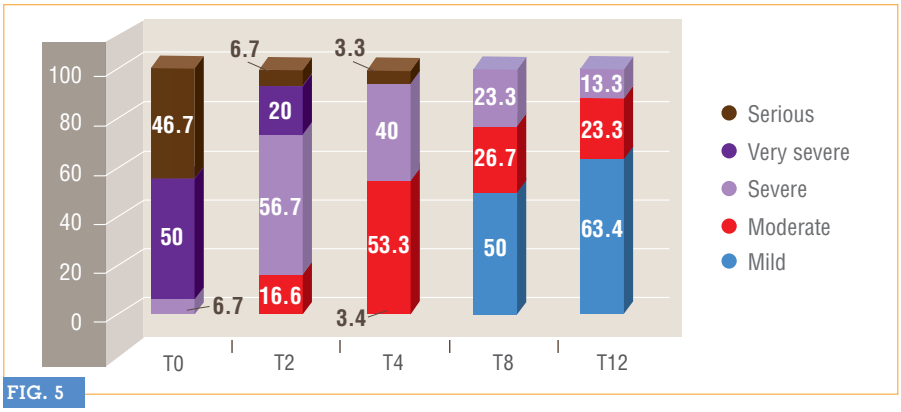


FIG. 5

Degree of knee joint damage on the Lequesne scale in GO-ON group.

– Results of treatment on a Lequesne scale

The rate of very severe in the MD-Knee group at T0 was 46.7% and 50% in the GO-ON group; after 2 weeks the rate was reduced to 6.7% and 20%, and further decreased in subsequent weeks. After the 12th week the level of severe and very severe is 0%. There is no difference between the 2 groups ($p > 0.05$) (FIGG. 4, 5).

– Results of the treatment on knee motor function

The rate of improvement of the knee-folding amplitude of the MD-Knee group at the time of T2 was 6.7% and at time of T12 was 43.3%. There has not been a correlation between demographic factors and clinical symptoms to the rate of improvement of the knee-folding amplitude at the time of 12 weeks following treatment ($p > 0.05$).
The rate of improvement in two MD-Knee and GO-ON groups were not statistically significant ($p > 0.05$).

– The rate of post-treatment patient's satisfaction after 3 months

The rate of satisfied and very satisfied patients in the MD-Knee group was 33.3% and 60% after 3 months of treatment respectively. There is no difference between the 2 groups ($p > 0.05$).

– Side effects

The only undesirable effect was tightness in the knee joints after injection (3.3%).

DISCUSSION

Assessing effectiveness on the VAS scale

In the MD-Knee group the pain level is markedly improved after 2 injections ($p < 0.05$), with an average VAS score decreasing to 3.77 versus T0. The improvement of the VAS scale is maintained, until week 8 and week 12. The 30% improvement rate of VAS, at T2 in the MD-Knee group was 16.7%, and 86.7% at T12.

This suggests that the analgesic effect lasts up to week 12 in the MD-Knee group.

The pain reduction was fast, strong, and lasting equally in both MD-Knee and GO-ON groups. Martin-Martin *et* Al. (6) using MD Knee in the treatment of knee osteoarthritis also showed an improvement in the average VAS pain scale; pretreatment was 7.5 and after 3 months of treatment was 5.26. Reshkova evaluated the efficacy of MD-Knee intraarticular injection and MD-Muscle pariarticular injection in 30 patients with knee osteoarthritis stage 2-3.
The author *et* Al. also showed a pronounced reduction in VAS average points: 7.32 before treatment, 4.32 after 2 months and 3 after 3 months of treatment.

These results are similar in comparison to our results. Nestorova *et* Al. (4) review ed the efficacy of MD-Knee and MD-Matrix IA injections on 25 patients with knee osteoarthritis even at later stages (phase 3,4) and showed a pronounced improvement in pain and motor indicators after 2 months and 3 months.
The VAS scale improvement in our GO-ON group was equivalent to the result of Pho, studying 151 knee osteoarthritis patients (7).

Evaluating the effectiveness of treatment on the WOMAC scale

The scores of WOMAC pain, stiffness, mobility and total were improved on MD-Knee group starting from the second week, markedly from the 4th week, until to T12. The improvement was similar to the GO-ON group.

Evaluating the effectiveness of treatment on the Lequesne scale

The Lequesne scale begins to improve in both MD-Knee and GO-ON groups from week 2, significantly from week 4 and continuously until the 12th week after treatment. The difference between the two groups is not statistically significant ($p > 0.05$).

The Lequesne scale improvement observed in two subgroups with 2 and 3 Xray stages and lasts up to 12 weeks.

The results of our research on GO-ON group were similar to Martin-Martin *et* Al. (6) (2016) and to Pho (7) studies.

CONCLUSIONS

MD-Knee intraarticular therapy has analgesic effect and improves motor function in the treatment of the primary knee osteoarthritis.

Paper presented at the 2nd INTERNATIONAL CONGRESS "COLLAGEN IN THE PATHOLOGIES OF THE MUSCULO-SKELETAL APPARATUS - Painful diseases of Joint & Muscle System. Important contribution of Collagen Medical Devices"

Milan, 16th November 2019

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COLLAGEN THERAPY IN LUMBAR SPONDYLOSIS. DOES THE METHOD OF ADMINISTRATION MATTER?

– A PILOT STUDY

SUMMARY

Objective: Comparison of the effectiveness of collagen injections with three methods of administration in the treatment of low back pain (LBP) in lumbar spondylosis.
Materials and methods: Randomized prospective study, 30 patients with lumbar spondylosis were assigned to 3 groups: subcutaneous (group A, n = 10), periradicular (group B, n = 10), and epidural (group C, n = 10).
Collagen injections were carried out once a week (in total 4 injections).
Assessment: Visual Analogue Scale (VAS) (0-10), Oswestry scale (0-50), Laitinen scale (0-16), One Leg Stence Test (OLST) – time to occurrence of pain in the support limb.
Endpoints: start of therapy (W0), end (W1) and 1 month after its completion (W2).
Results: An improvement was obtained in all the 3 methods of collagen Medical Devices administration. Minimal clinically important difference (MID) i.e. 3 points on the VAS scale was observed in 44% of patients in group A, 40% of patients in group B and 60% in group C. MID on the Oswestry scale determined at 10 points was obtained respectively in 56%, 50% and 20% of patients, while MID for Laitinen scale determined at 4 points was obtained in 56%, 30% and 40% of patients, respectively.
Only in the A group all treated patients achieved a reference value of 30 seconds for OLST.
Conclusions: Subcutaneous administration collagen is not inferior in terms of effectiveness to periradicular and epidural injections in the treatment of LBP in lumbar spondylosis.

KEY WORDS

CHRONIC LOW BACK PAIN, CHRONIC PAIN TREATMENT, CHRONIC PAIN, PAIN CONTROL, MEDICAL DEVICE INJECTIONS

INTRODUCTION

Low back pain (LBP) is one of the 10 most common diseases of civilization, covering, as estimated by WHO, 60-70% of the population in developed countries with an annual prevalence of 15-45% adults and an annual incidence of 5% (1).

The mechanism of pain in the lumbar region is a very complex process. Anatomical pain generators are well known because intervertebral discs, *dura mater*, facet joints, and paravertebral soft tissues have nociceptive innervation. Pain conduction pathways are also well known, but the mechanisms of disturbed "processing" of the pain signal at the level of the dorsal root ganglion, spinal cord or cerebral centers, and the associated sensitization processes leading to pain chronicization are still the subject of intensive study (2).

The experience of Pain Medicine in research on the administration of synthetic drugs on the example of local anesthetics and steroids leads to linear thinking - the precision of access to pain generators and strictly defined dosage are a condition of treatment effectiveness and determine the strength of the therapeutic effect (3).

– For collagen, the same paradigm no longer seems so obvious, because clinical experience shows that some patients have remarkable improvement even after subcutaneous administration of collagen in the lumbar spine, which seems to be away from major pain generators.

Even in the case of very advanced degenerative processes, in addition to reducing pain, it is also reported functional effects such as obtaining upright posture, increasing flexibility and improving overall mobility.
This suggests that collagen is not an ordinary drug that works on a complementary basis with a specific receptor, causing a therapeutic effect proportional to the dose and local availability, but rather it is a catalyst for change, a biologically active substance that triggers a cascade of repair processes. The following arguments support the use of injectable collagen in the treatment of low back pain:
1) inflammatory process associated with discogenic instability is always associated with an increased collagen biodegradation, the supply of exogenous collagen reduces the negative balance of production and biodegradation;
2) collagen fulfills the role of a biological medium (bio-scaffold) for cell colonization producing a tissue signal promoting healing (monocytes, platelets, macrophages, fibroblasts);
3) collagen has spasmolytic and anti-edema effects through the barrier effect;
4) exogenous collagen, provides a substrate for the production of new collagen chains; on the one hand, it contributes to the stabilization of capsule and ligament structures, and on the other, it improves mobility through fascia reorganization (4,5,6).

– The aim of this study was to check whether the administration of collagen in the immediate proximity of pain generators (periradicular, epidural) improves its effectiveness in comparison with the superficial (subcutaneous) administration of the same dose.

MATERIALS AND METHODS

The study was single-center, prospective, randomized and open.
– Inclusion criteria: adult patients, positive signs and symptoms in a clinical examination, lumbar spondylosis with foraminal stenosis confirmed by X-ray or MRI; no other treatments in the last 6 weeks.
– Exclusion criteria: systemic diseases (inflammatory, infectious or neoplastic), recent injuries, surgery and neurological deficits.

The assignment to **3 groups** with different collagen administration techniques was performed with simple randomization based on a computer-generated randomization list. All injections were always administered by the same physician.
Group A – subcutaneous injections in the line of facet joints, paravertebral, multipoint technique.
Group B – periradicular injections under ultrasound control, in-plane technique.

	All patients, n	Group A	Group B	Group C
N (total)	30	10	10	10
F	19 (63,3)	6	8	5
Age, average (SD)	62,6 (13,7)	62,0 (16,1)	68,1 (13,4)	57,6 (10,2)
Duration of complaints, weeks, average	11,7 (14,2)	6,3 (8,3)	12,1 (11,3)	16,6 (19,9)
Range	1 - 52	1 - 28	3 - 32	1 - 52
Period of disease				
Acute	16 (53,3)	7	4	5
Subacute	4 (13,3)	1	3	-
Chronic	10 (33,3)	2	3	5
Level of foraminal stenosis				
L3/L4	2 (6,7)	2	-	2
L3/L4, L4/L5	1 (3,3)	-	-	-
L3/L4, L4/L5, L5/S1	3 (10,0)	-	2	-
L4/L5	2 (6,7)	1	-	1
L4/L5, L5/S1	8 (26,7)	4	2	4
L5/S1	14 (46,7)	3	6	3
Painful side(s)				
left	9 (30)	3	4	3
right	8 (26,7)	2	4	2
both	13 (43,3)	5	2	5

TAB. 1

Characteristics of the study groups.

Group C – epidural, interlaminar approach injections under ultrasound control.

A collagen mix containing 2 vials of **MD-Neural** and 1 vial of **MD-Lumbar** per session was administered, and if the complains were bilateral, injectate was administered bilaterally in groups A and B.

Frequency of injections: 1/week (4 sessions in total).

Endpoints: W0 (before treatment), W1 (end of therapy - after 4 weeks), W2 (after 1 month of observation).

Control tools: Visual Analogue Scale **(VAS)** (0-10), **Oswestry** (0-50) and **Laitinen** (0-16) questionnaires completed by the patient, **One Leg Stence Test** (OLST) (0-30 seconds) with measurement always carried out by the same physician (7).

Descriptive statistics (mean, standard deviation, frequencies) were calculated in StatsDirect statistical software version 2.8.0. In assessing the effectiveness of treatment, the value of minimal important difference (MID) was used.

A change of MID on the VAS scale was set to 3 points, for the Oswestry scale to 10 points, for the Laitnen scale 4 points, and for the OLST test as a reference value indicating the normal state, a time of ≥30 seconds was used (8,9).

Each patient qualified for the study received very accurately, giving written information about its purpose, injection technique and possible risk of complications. Written consent to participate in the study was obtained from each patient and personal data protection was ensured.

RESULTS

Between May and July 2019, **30 patients** (19 F and 11 M; mean age 62.6) were included in the study.

The average duration of the complaints was 11.7 weeks (range from 1 to 52 weeks).

The study groups were similar to each other except for the duration of the discomfort (mean 6.3 weeks in group A *vs.* 16.6 weeks in group C).

The detailed characteristics of the study

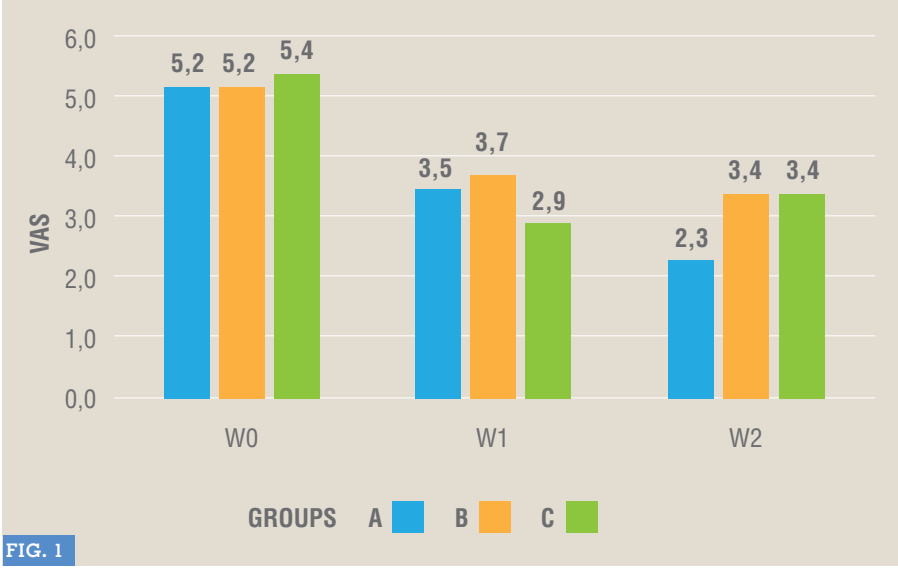

FIG. 1

Average Visual Analogue Scale (VAS) values at control points.

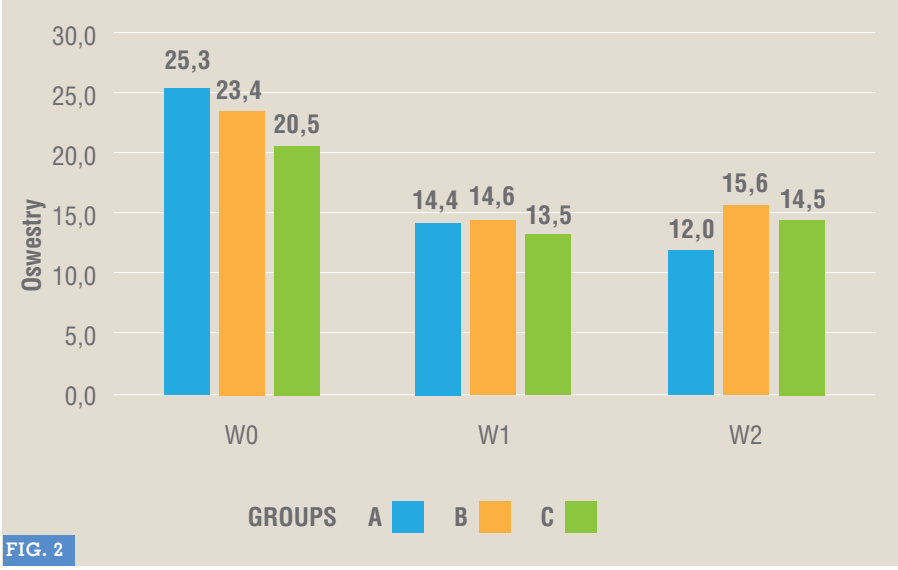

FIG. 2

Average Oswestry questionare values at control points.

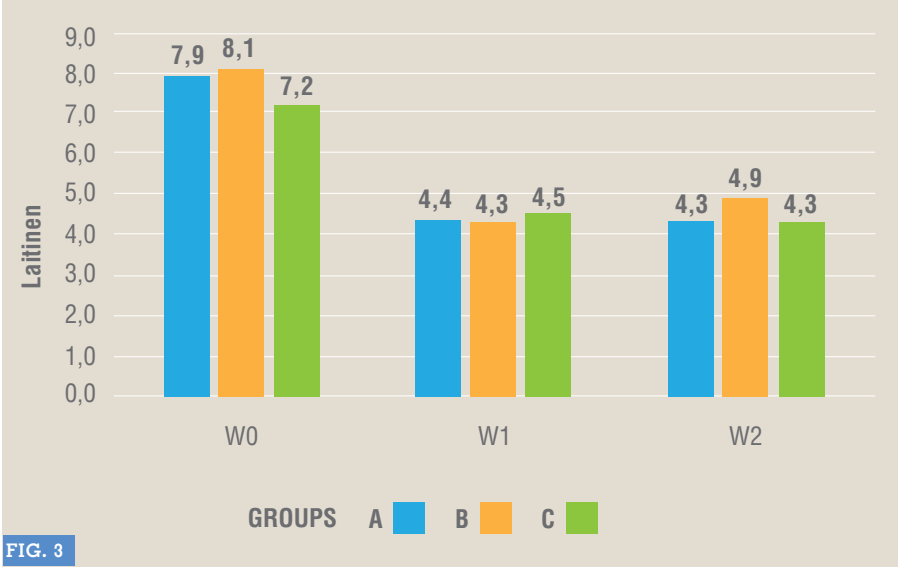

FIG. 3

Average Laitinen questionare values at control points.

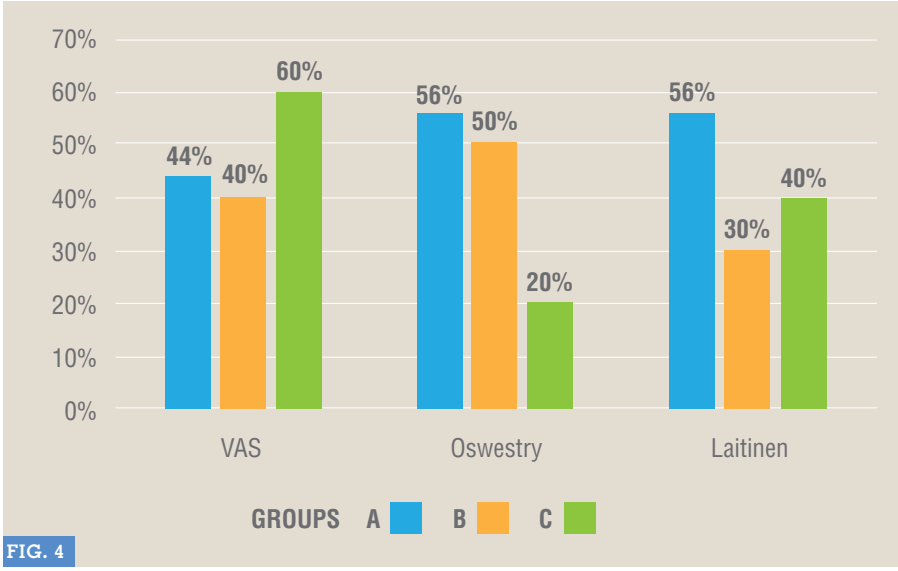

FIG. 4

Percentage of patients achieving minimal clinically significant difference (MID) in individual study groups.

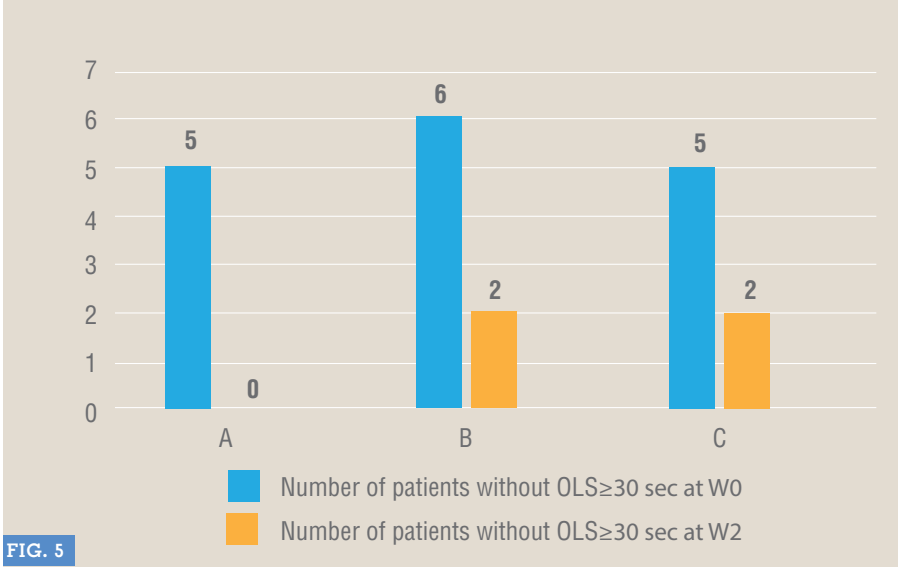

FIG. 5

Number of patients without OLST ≥30 seconds at control points W0 and W2.

group are presented in TAB. 1.
All patients who started the study received a full dose of treatment and had a W1 control visit.
One person (from group A) was not included in the W2 follow-up visit because of surgical treatment in the field of lower limb arterial surgery during the observation period.
The changes in the mean VAS values and scoring of the Oswestry and Laitinen scales in individual groups are shown in FIGG. 1, 2, 3.

The percentage of patients who obtained the accepted values of MID was analysed in all groups.
The highest percentage of MID change on the VAS scale was obtained in group C (60%), while the highest percentage of MID change on the Oswestry and Laitinen scale was obtained in group A (56%) (FIG.4).
In the OLST functional test, the number of patients who did not reach the OLST reference value (≥30 seconds) at the W2 checkpoint in each group was recorded (FIG. 5).

There were no side effect of Collagen Medical Devices in the studied groups of patients.

There were two cases of mild punctional syndrome with transient headaches in the epidural group and one worsening of pain in group A during the treatment alone (between dose II and III); this event did not require discontinuation.

DISCUSSION

Improvement was observed in all groups treated with collagen injections.

– The highest percentage of patients achieving minimal clinically significant change in the Oswestry and Laitinen scales was observed in the subcutaneous supply group, and the VAS scale in the epidural supply group.

The advantage of the study is its randomized and prospective nature. At the same time, the small number of patients studied remains the biggest limitation. As a consequence, classical statistical analysis was abandoned in favor of calculating the percentage of patients reaching MID in terms of endpoints.
The study should be considered as a pilot study and may be the basis for estimating the size of the sample of a proper, randomized clinical trial in the assessment of the effectiveness of collagen therapy.

Pavelka *et* Al. compared the effectiveness of subcutaneous injections of a mix containing collagen MD-Lumbar, MD-Muscle, and MD-Neural with mesocaine in a group of 48 patients, obtaining comparable effects over a 5-week observation period. The authors emphasize the good safety profile of the preparations (10,11).
Additive injections have a completely different application of collagen injections in the experimental treatment of low back pain, where the authors hope to restore the structural framework of the fibrous ring of the intervertebral disc, but these studies do not go beyond the phase of the animal model and *in vitro* (12,13).
To the author's knowledge, however, there are no publications that would re-

port the use of collagen in periradicular or epidural administration as an option for conservative treatment of LBP.
The explanation of collagen principle of operation in such an application should be subject to further research, as it may be a very interesting option for the treatment of LBP with a stiffness component.

CONCLUSIONS

1) Collagen administred by injection shows a high safety profile.
2) Regardless of the method of administration, paravertebral collagen injections show an analgesic effect and also improve mobility in patients with foraminal stenosis in the course of lumbar spondylosis in the short observation period.
3) Collagen administered subcutaneously form seems to be of particular interest as a therapeutic option in patients with foraminal stenosis in the course of lumbar spondylosis, showing no less analgesic effect and functional improvement than in periradicular and epidural injections, with no risk associated with the technique of administration.
4) Due to the limited size of the study group, the obtained results should be treated as preliminary. They require confirmation in randomized clinical trials on a larger group of patients. ■

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Milan, 16th November 2019

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CLINICAL

E. Milano

COLLAGEN MEDICAL DEVICE LUMBAR IN THE COMBINED TREATMENT OF LUMBAR INSTABILITY-INDUCED PAIN

SUMMARY

Spondylolisthesis is a mechanical alteration in the physiological vertebral structure that is primarily characterised by the forward displacement of a part of or whole vertebra on to that below.
The L-S rachis segment is mostly interested.
There are 3 kinds of Spondylolisthesis: dysplastic, due to osteo-articular congenital alterations; isthmic, characterized by a continuous lesion of the isthmus; degenerative.

– The aim of this study is to verify if a combined treatment, Physiokinesitherapy + ultrasound-guided injection of Collagen MD (Medical Device)-Lumbar, may provide more important and durable clinical results rather than Physiokinesitherapy alone.
– 20 patients, F and M, aged between 40 and 75, have been enrolled; all of them suffering from grade 1 and 2 Spondylolisthesis.

They were randomised to 2 Groups (10 + 10 patients), a treated Group (T) and a control Group (NT).
– The clinical results, evaluated at 2, 4, 8 and 12 months with the Numeric Rating Scale, the Oswestry Disability Index, the Pain Disability Index and the use of NSAIDs (number of tablets/week), allow to state that the combined treatment Physiokinesitherapy + MD-Lumbar obtains a far better and longer-lasting improvement than Physiokinesitherapy alone.

KEY WORDS **SPONDYLOLISTHESIS, MEDICAL DEVICE LUMBAR, COLLAGEN, ARTHROSIS**

INTRODUCTION

Spondylolisthesis (SL) [from the Greek *spóndilos* (vertebra) and *ólístesis* (slipping)] is a mechanical alteration in the physiological vertebral structure that is primarily characterised by the **forward displacement** (anterolisthesis) of a part of or whole vertebra onto that below.
– Although SL can affect any segment of the spine, it is the lumbar segment that is most commonly affected.

Various authors have estimated the incidence of SL in the general population to be **3-8%**; however, it can affect up to **20%** of the individuals involved in occupational activities or sports requiring hyperlordosis (e.g. artistic gymnastics, gymnastic rings, diving, golf) or in the handling of heavy loads (e.g. weightlifting).

– Clinicians are often called on to identify the origin of spinal pain and equally frequently forget that even a moderate spinal microinstability, such as SL, may be the cause.

One particularly important anatomical point in SL is the vertebral isthmus, the element between the superior and inferior apophyses that forms a connection

between the anterior and posterior portion of the vertebra.

Undoubtedly, one of the least resistant points of the spine is the **lumbosacral junction (L5-S1)**, where the slope of the upper surface of S1 tends to cause the body of L1 to slip downwards and forwards.
– This displacement is restricted by the anatomical connections of the posterior arch of L5 and, in particular, by the isthmus.

– SL occurs when the isthmus is subject to interruption or destruction.
Furthermore, in addition to the osteoarticular structures, whose focal point are the spinal facet joints, seat to inflammatory processes developed over time driven by the pro-inflammatory cytokine network, the tendinous and ligamentous structures (e.g. the yellow ligament), the capsular structures, the intervertebral disc, the muscle structures (the multifidus muscle and the iliopsoas muscle) and the deep *fasciae* structures are also involved in the origin of SL-induced pain (mechanical low back pain).

• There are 3 main types of SL:

DYSPLASTIC

The dysplastic form is secondary to congenital osteocartilaginous alterations in the isthmus and consists of 2 main subtypes:

1) the form that is secondary to the sagittal orientation of the articular apophyses of S1 that lose contact with L5, which therefore slips forward;
2) the form that is secondary to the pathological elongation of the isthmuses of L5.

ISTHMIC

In most cases **(80%)**, idiopathic bilateral isthmic lysis involves L5 and it is characterised by a fracture of the isthmus, which causes an increase in the size of the spinal canal, as the posterior portion remains in place

The inter-articular portion (i.e. isthmus) is the point of least resistance subject to continuous microtraumas that, together with other environmental and genetic factors, reduce its mechanical resilience.

– During development, isthmic SL often occurs following a minor trauma, thus revealing the underlying malformation.
The signs and symptoms differ from those observed in adults; young patients experience mild pain without any specific topographical location, even in the presence of significant anterior displacement.
– In some cases, the only sign is hypertonia of the posterior thigh muscles, making it difficult to flex the limb at the hip with the knee extended.

DEGENERATIVE

The degenerative form is very common and is often little considered, partly due to the minimal likelihood of efficacious treatment, which constitutes the **target of this study**.

– Unlike isthmic SL, the degenerative form causes a reduction in the dimensions of the spinal canal; the favouring factors are the degeneration of the disc and of the articular apophyses, and an excessively vertical orientation of the articular apophyses.

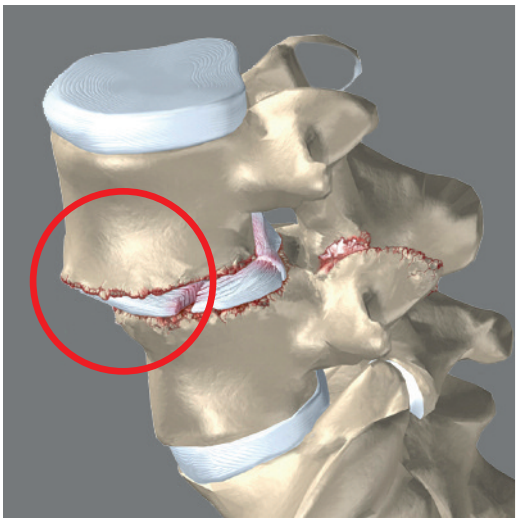
In addition to low back pain, it can also be associated with neurogenic claudication caused by spinal canal stenosis.

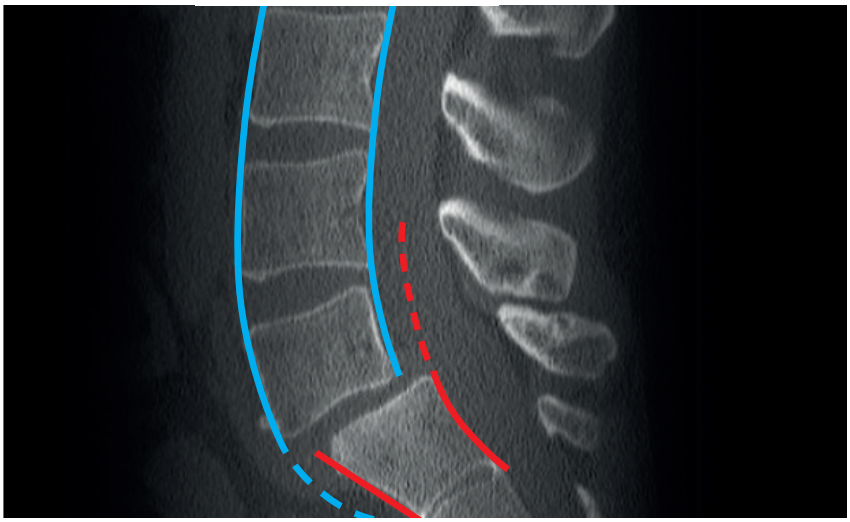
Degenerative SL affects adults; it is caused by long-standing spinal instability and by alterations secondary to the abnormal displacement of the unstable segments, i.e. **osteoarthritis** and/or **degenerative disc disease**.

This form is **4-6** times more common in **females** and affects L4 10 times more frequently; the anterior displacement can be up as much as 33%.

The degree of displacement is primarily assessed using the Meyerding Grading System, which classifies it into 4 grades:
in grade **1**, the displacement is equal to less than 25% of the upper surface of S1;
in grade **2** it is less than 50%;
in grade **3** it is less than 75%;
in grade **4**, the entity of the forward displacement can exceptionally reach 100%, with the potential displacement of L5 in the pelvis (Spondyloptosis).

– The intervertebral disc is inevitably involved; as it is no longer protected by the posterior structures, it absorbs functional overloads that exceed its anatomical characteristics, causing it to undergo a degenerative process that leads to flattening and, eventually, to herniation with an exacerbation of the pain symptoms of SL.





The nerve components are often involved with the compression of the dural sac and of the nerve roots of L5 and S1.

The severity of the SL does not often correlate with the intensity of the pain symptoms.

– The symptoms of SL are **1)** mechanical low back pain, which is made worse by movement and improves with rest;
2) irradiation of pain to the lower limbs.

– Patients often experience a worsening of the pain when changing posture (from sitting to standing).
The following symptoms are less common: discogenic low back pain that gets worse when seated and with the forward flexion of the upper body; facet joint pain that gets worse with the hyperextension of the upper body and when standing; neurogenic claudication (lower extremity asthenia when walking) caused by the spinal canal stenosis that is often present.

– Anteroposterior, laterolateral and oblique projection x-rays, in addition to a dynamic x-ray study in the position of maximum anterior flexion and maximum extension, are essential for the diagnosis of SL.
MRI is used to evaluate the possible compression of the nerve roots and any disc degeneration and/or bulging.

It is not always simple to correlate instability (such as moderate degenerative SL) with pain symptoms and it is even more arduous to identify **degenerative microinstability** at an early stage.

The real problem, however, is efficacious conservative treatment.

Most patients with SL can be treated conservatively, especially in the presence of the grade 1 and 2 degenerative forms, in which the displacement evolves in approximately **50%** of cases, depending on the case histories considered.

The conservative treatment of SL is essentially physiotherapy-rehabilitation-based: the aim is not only to strengthen the muscles of the upper body in order to stabilize the spine, but also to improve the neuromotor and proprioceptive control of the pelvic girdle muscles, antigravity muscles and respiratory muscles.

– It is, of course, essential to re-educate the patient on how to maintain a good static and dynamic posture.

In the acute phase, when the clinical situation is characterised by persistent low back pain, it is necessary to observe a suitable period of bed rest, associated with the administration of conventional and/or low-dose anti-inflammatories and muscle-relaxants, either individually or in combination.

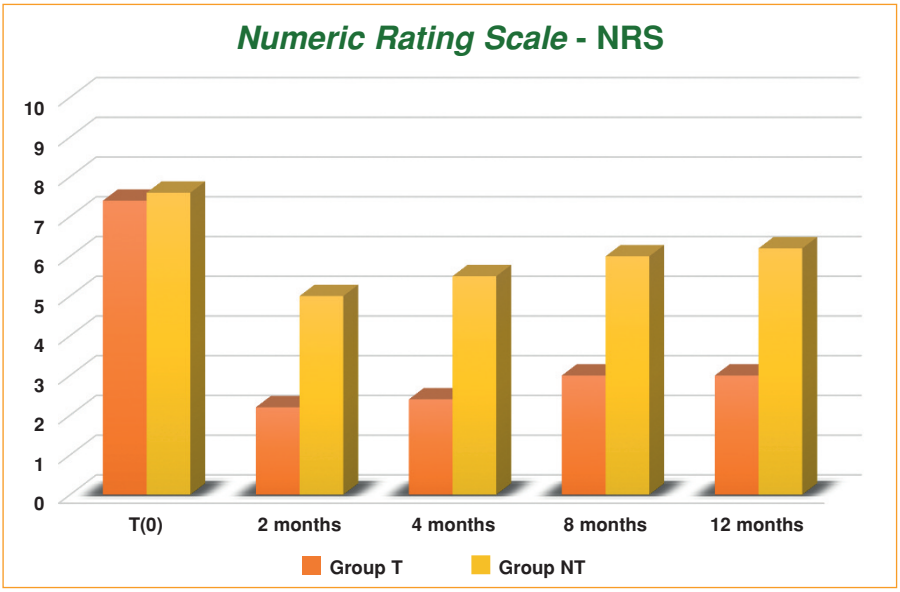
The optimisation of the conservative treatment of low back pain secondary to degenerative SL, taking into account all the anatomical structures involved in this aetiopathogenesis, allows to formulate a number of considerations.

COLLAGEN MEDICAL DEVICES

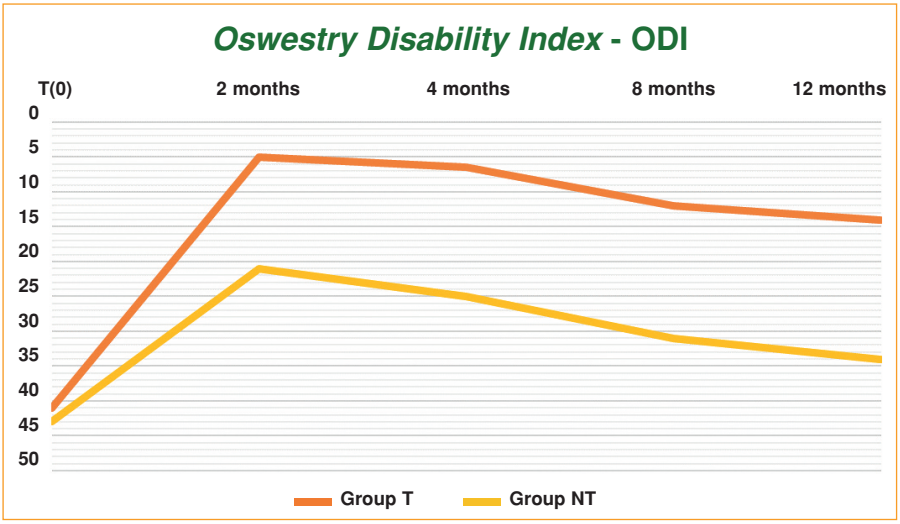
The use of injectable medical devices **(MD)** containing porcine collagen allows a more efficacious and specific *in loco* positioning of the collagen, with a carrier and stabilisation function.

– It makes it possible to replace, strengthen, structure and protect the cartilage, tendons, ligaments and joint capsules, thereby optimising the structure of the collagen fibres and of all the extra- and intra-articular structures in which it is present, thereby providing a mechanical support to the anatomical district in question.

The hypothesis of the study was that a treatment with a specific injectable Collagen MD could re-condition the anatomical structure/s impaired by SL and improve the stability of the lumbosacral spine; that a "combined" treatment would have been able to improve the functional rehabilitation outcomes and/or provide more efficacious pain control in the subacute and chronic phases; and that a combined treatment would also have been able to positively

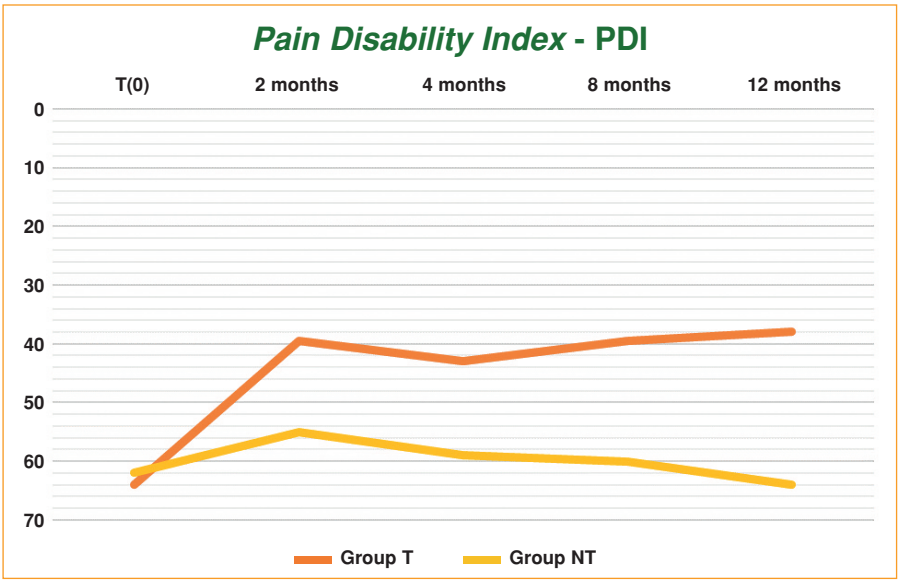


TAB. 1



TAB. 2

TAB. 3



condition the progression of SL with less frequent exacerbations.

MATERIALS AND METHODS

In order to explore this hypothesis, **20 patients** with Physical Medicine outpatient clinic appointments for low back pain were recruited and included in the study, from January 2018 to January 2019.

– The patients were randomised to 2 treatment groups [**T** Group (**Physiokinesis therapy** + ultrasound-guided injections of **MD-Lumbar**) and the **NT** Group (**Physiokinesis therapy** alone)], stratified by age and gender; the outcomes were assessed at **2**, **4**, **8** and **12 months**.

– Inclusion criteria

F and M patients aged between 40 and 75 years; clinical and instrumental diagnosis of **grade 1** and **grade 2 Spondylolisthesis**; NRS (Numeric Rating Scale) **> 5**, no use of NSAIDs, corticosteroids or opioids.

– Exclusion criteria

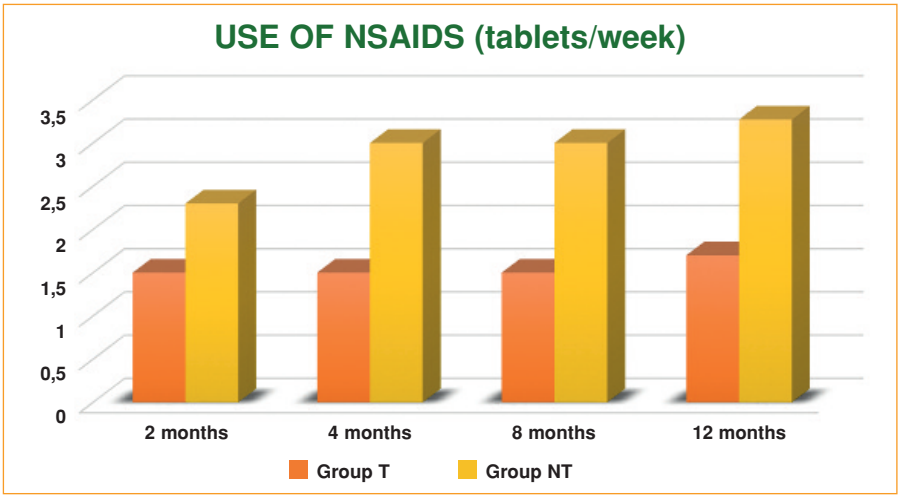
Rheumatoid arthritis, chondrocalcinosis, psoriasis, metabolic bone diseases, gout, active infections, clinical and instrumental diagnosis of grade 3 and grade 4 spondylolisthesis, spondylolysis, polyneuropathy, previous local/epidural corticosteroid injections (> 3 years), use of oral corticosteroid and/or opioid therapy in the past 6 months, use of anticoagulants, pregnancy, mental diseases.

Both the T and the NT Groups were administered the same intra-hospital rehabilitation protocol (diagnostic and therapeutic care programme) based on neuromotor treatment for the proprioceptive reconditioning of the posterior back, lumbosacral girdle and respiratory muscles.

– The protocol also included ergonomic education and occupational therapy.

The rehabilitation treatment consisted in:
daily individual motor rehabilitation treatment for a total of ten 45-minute sessions; individual assessment
by the occupational therapist at the 5th and 10th session; provision of a brochure illustrating the physiokinesis therapy exercises to be performed by patients at home and ergonomic advices; group treatment (max. 4 patients) one month after the last individual session, on 2 consecutive days, in 30-minute sessions.

• **Group T** (Treatment) also received ultrasound-guided injection therapy (Clarius Ultrasound portable system, Convex probe) according to the following protocol:
5 sessions (1/week for 4 consecutive weeks and 1 after 15 days); **2 vials** of **MD-Lumbar** per treatment.
– Half a vial (1 mL) for each facet joint; 2 joints were treated at each treatment, alternating the upper and lower facet joints; at the 5th session the 2 most impaired joints (as shown by MRI) were treated.



TAB. 4

A number of clinical and functional outcomes were investigated:
1) Numeric Rating Scale **(NRS)**
2) Oswestry Disability Index **(ODI)**
3) Pain Disability Index **(PDI)**
4) use of NSAIDs during the follow-up period (TABLES 1, 2 ,3 and 4).

CONCLUSIONS

The data obtained (TAB. 5) allow to conclude that in the treatment of grade 1 and grade 2 Spondylolisthesis combined treatment with physiokinesis therapy + injection of MD-Lumbar makes it possible to obtain a far **better** and **longer-lasting improvement**, in terms of
1) pain
2) motor function
3) impairment caused by spinal instability
4) reduced use of NSAIDs.

Furthermore, the combined treatment proposed herein, for the first time in the

OUTCOMES	T (0)		2 months		4 months		8 months		12 months	
GROUPS	T	NT	T	NT	T	NT	T	NT	T	NT
NRS *Numeric Rating Scale*	6,9	7,1	1,7	4,5	1,9	5,0	2,5	5,5	2,5	5,7
ODI *Oswestry Disability Index*	41,0	42,0	5,0	21,0	7,0	25,0	12,0	31,0	14,0	34,0
PDI *Pain Disability Index*	64,0	62,0	40,0	56,0	42,0	58,0	40,0	60,0	38,0	64,0
NSAIDs *tablets/week*			1,3	2,0	1,3	2,7	1,3	2,7	1,4	3,0

TAB. 5

From the data obtained, it emerges that:
– NRS. Group T (Physiokinesis therapy + ultrasound-guided injection therapy of MD-Lumbar) passes from 6.9 (T0) to 2.5 after 12 months (-63.8%). Group NT (Physiokinesis therapy alone) passes from 7.1 (T0) to 5.7 after 12 months (-19.7%).
– ODI. Group T passes from 41.0 (T0) to 14.0 after 12 months (-65.9%). Group NT passes from 42.0 (T0) to 34.0 after 12 months (-19.1%).
– PDI. Group T passes from 64.0 (T0) to 38.0 after 12 months (-40.6%). Group NT passes from 62.0 (T0) to 64.0 after 12 months (±0%).
– NSAIDs (tablets/week). Group T passes from 1.3 at 2 months to 1.4 at 12 months (±0%). Group NT passes from 2.0 at 2 months to 3.0 at 12 months (+50%).

treatment of Spondylolisthesis, would appear to allow a better control over disease progression and a reduction in exacerbations over time (pro-inflammatory cytokine network control).

• **MD-Lumbar** improves the stability of the lumbosacral spine and organically reconditions the impaired anatomical structures (joint capsules, yellow ligament, antigravity muscles and connective deep fascia), thereby making a considerable contribution to the promotion of neuromotor and proprioceptive capacity.

Over the next few months, we hope to be able to confirm the results obtained by expanding the study sample and, in particular, to identify the optimum timing for further injection therapy with MD-Lumbar as part of an individual maintenance rehabilitation programme.

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Fig. p. 40
https://urbanministries.com/wp-content/uploads/2019/01/iStock-927091262-Pain.jpg

Fig. p. 41
Left:
https://eorthopod.com/images/ContentImages/spine/spine_lumbar/lumbar_spondylolistheis/lumbar_spondylolisthesis_cause02.jpg
Right:
https://www.brainspinesurgery.com/uploads/img/_800xAUTO_crop_center-center_60/Spondylolisthesis-Spine-Condition-and-Symptoms-Xrayy.png

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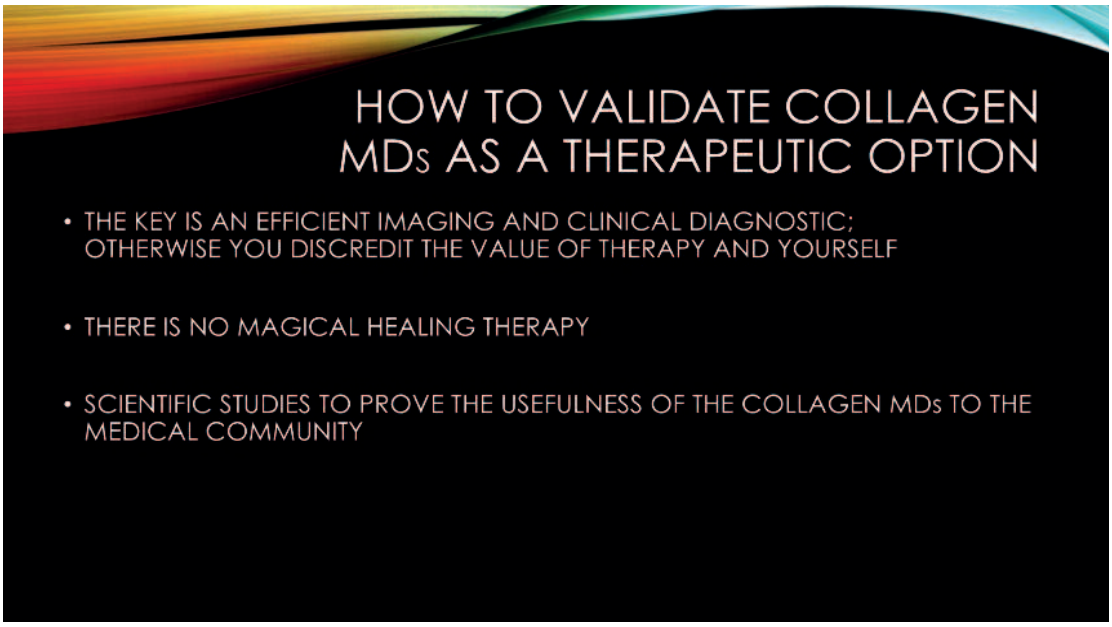
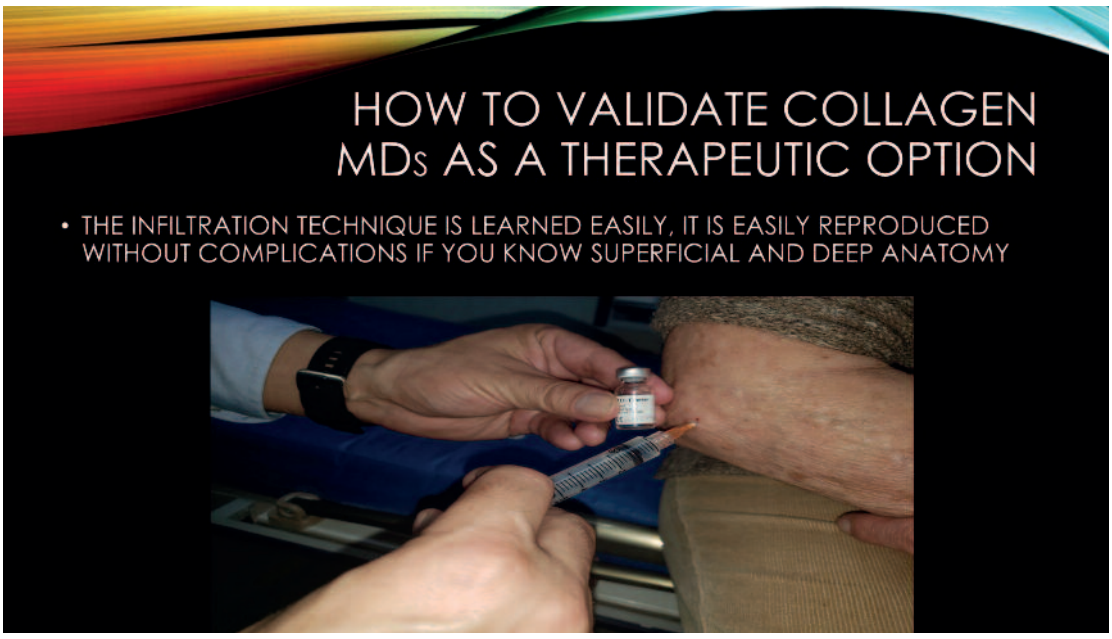
CLINICAL

O. Ahumada Arredondo

EPICONDYLITIS – A SOLUTION WITH COLLAGEN MEDICAL DEVICES





EPICONDYLITIS, WHAT'S ON

- IT IS FREQUENTLY ASKED BY PATIENTS
- IT IS RECORRENT
- SELF LIMITED IN 12 OR MORE MONTHS
- 20% OF EPICONDYLITIS ARE SECONDARY
- IT IS OPERATED IN NO MORE THAN 5% OF THE CASES
- TOO MANY TREATMENTS EXIST; IT IS A PROBLEM THAT DOES NOT KILL BUT IT IS EXTREMELY ANNOYING

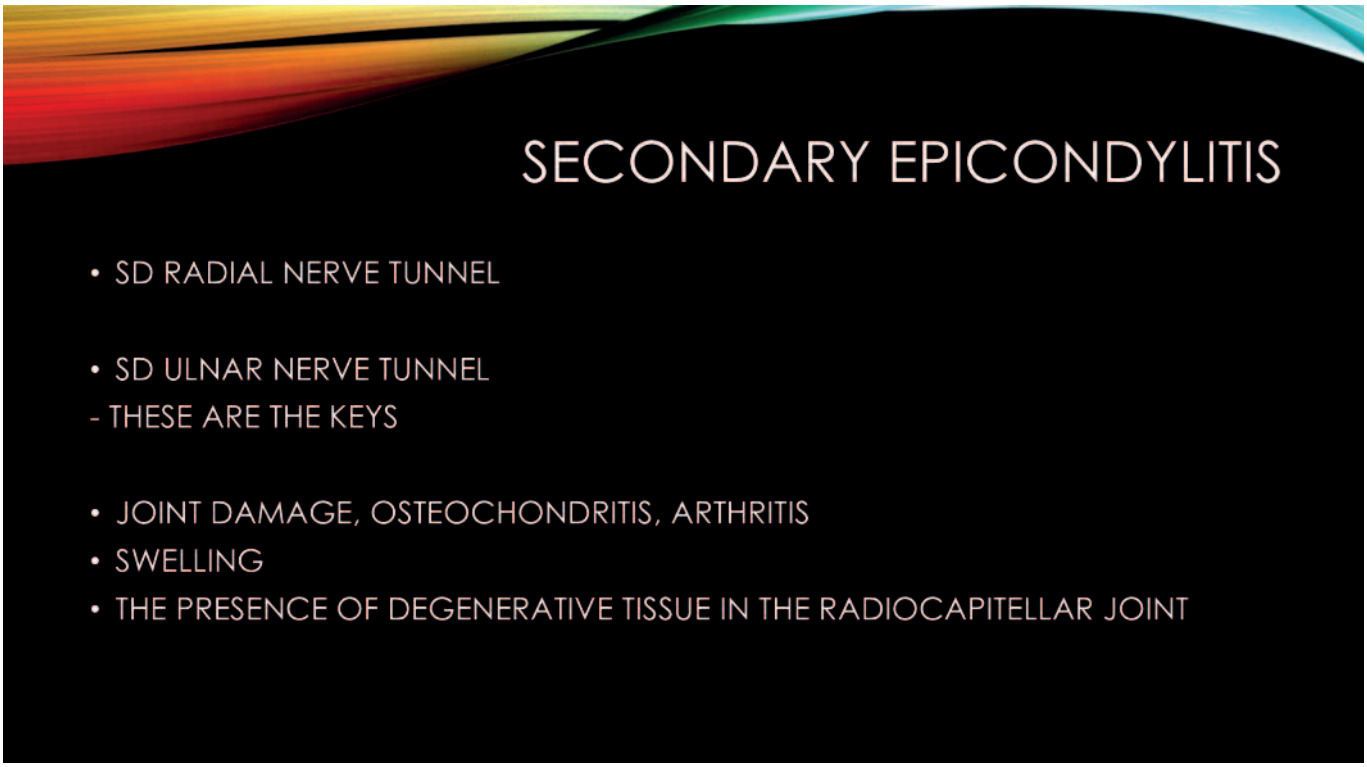
LET'S THINK

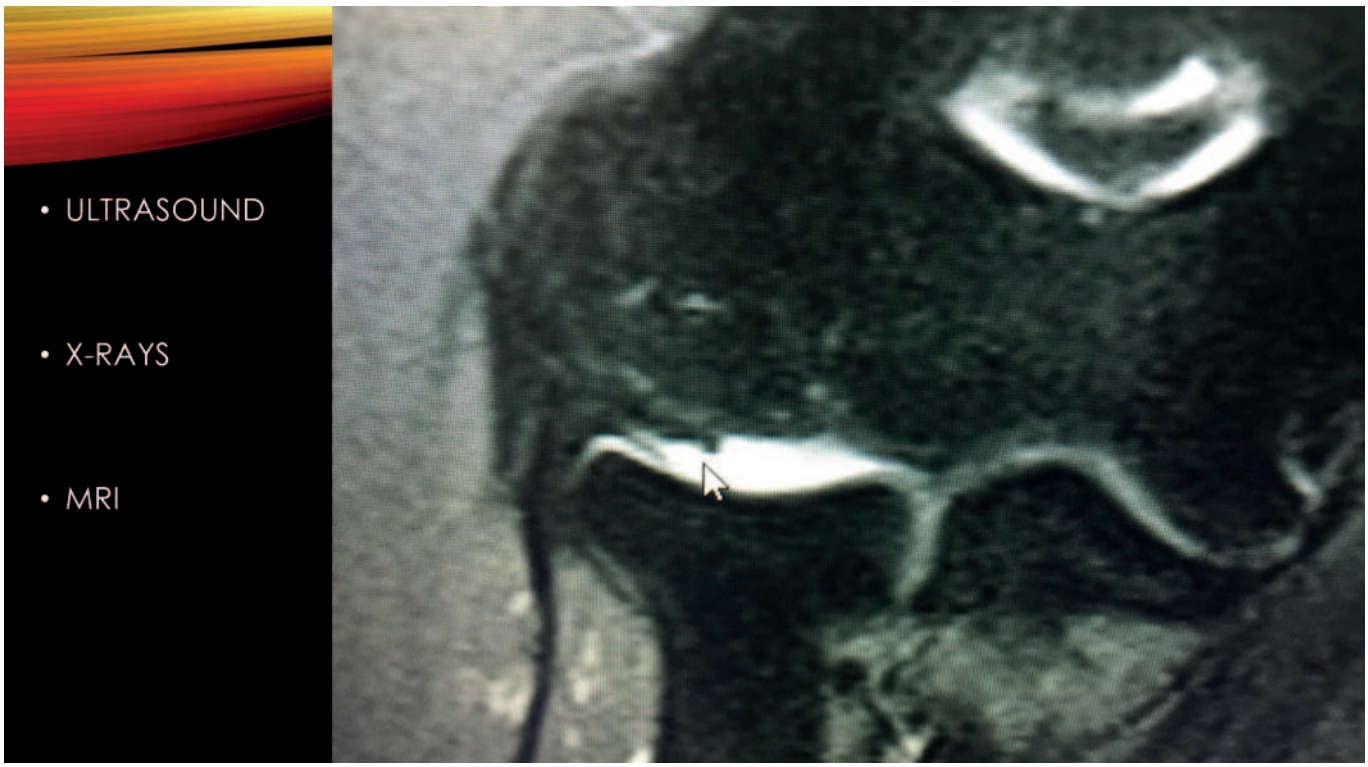
- THE ELBOW IS A BIOMECHANICAL POINT OF STRESS OF THE UPPER LIMB
- IF WE CONSIDER IT AS A LEVER, IT RECEIVES STRENGTH FROM ITS TWO OPPOSITE EXTREMES AND IT MUST REGULATE AND DISPERSE IT FOR THE CORRECT BALANCE OF THE FUNCTION TO BE PERFORMED


ANATOMY
Epicondylitis
Radial nerve compression
Radial head
Plica
OCD
Fig. 3 Location of the site of greatest tenderness may be helpful in defining the diagnosis for further clinical testing and/or imaging techniques.


NEUROANATOMY

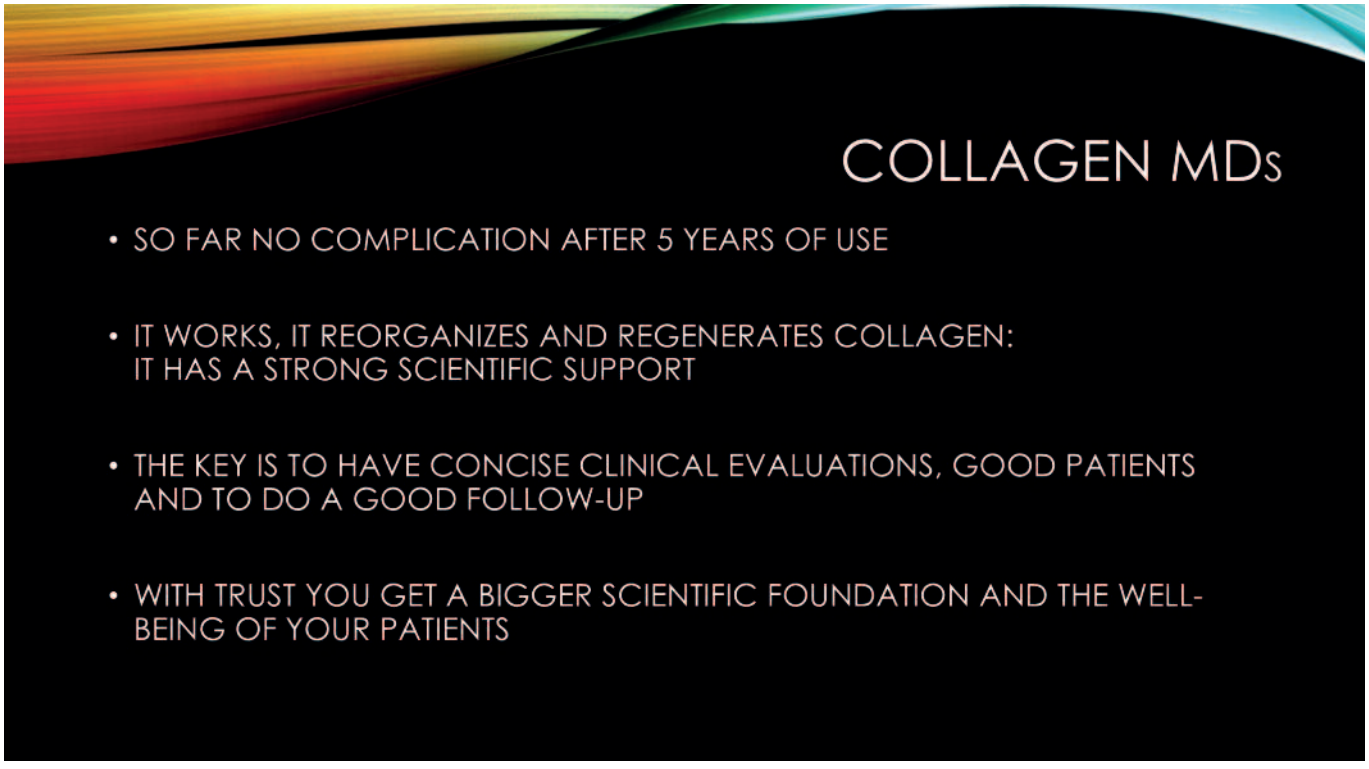

PRIMARY EPICONDYLITIS
• TENDINOSIS
• MUSCLE TEARING


SECONDARY EPICONDYLITIS
• SD RADIAL NERVE TUNNEL
• SD ULNAR NERVE TUNNEL
- THESE ARE THE KEYS
• JOINT DAMAGE, OSTEOCHONDRITIS, ARTHRITIS
• SWELLING
• THE PRESENCE OF DEGENERATIVE TISSUE IN THE RADIOCAPITELLAR JOINT


• ULTRASOUND
• X-RAYS
• MRI


WHY SO MANY RECURRENT CASES FOR SOMETHING SO LOCAL AND SIMPLE?
• MANY THERAPIES BUT TOO MANY FAILURES
• POOR DIAGNOSIS
• POOR STUDY OF THE DISEASE
• BIO-PSYCHO-SOCIAL RELATIONS


WHY COLLAGEN MDs?
• WHY NOT?
- IT IS SIMPLE
- BIOLOGICAL
- GOOD PRICE/QUALITY RATIO


COLLAGEN MDs
• SO FAR NO COMPLICATION AFTER 5 YEARS OF USE
• IT WORKS, IT REORGANIZES AND REGENERATES COLLAGEN:
IT HAS A STRONG SCIENTIFIC SUPPORT
• THE KEY IS TO HAVE CONCISE CLINICAL EVALUATIONS, GOOD PATIENTS
AND TO DO A GOOD FOLLOW-UP
• WITH TRUST YOU GET A BIGGER SCIENTIFIC FOUNDATION AND THE WELL-
BEING OF YOUR PATIENTS

RESULTS OF PARTIAL FOLLOW-UPS

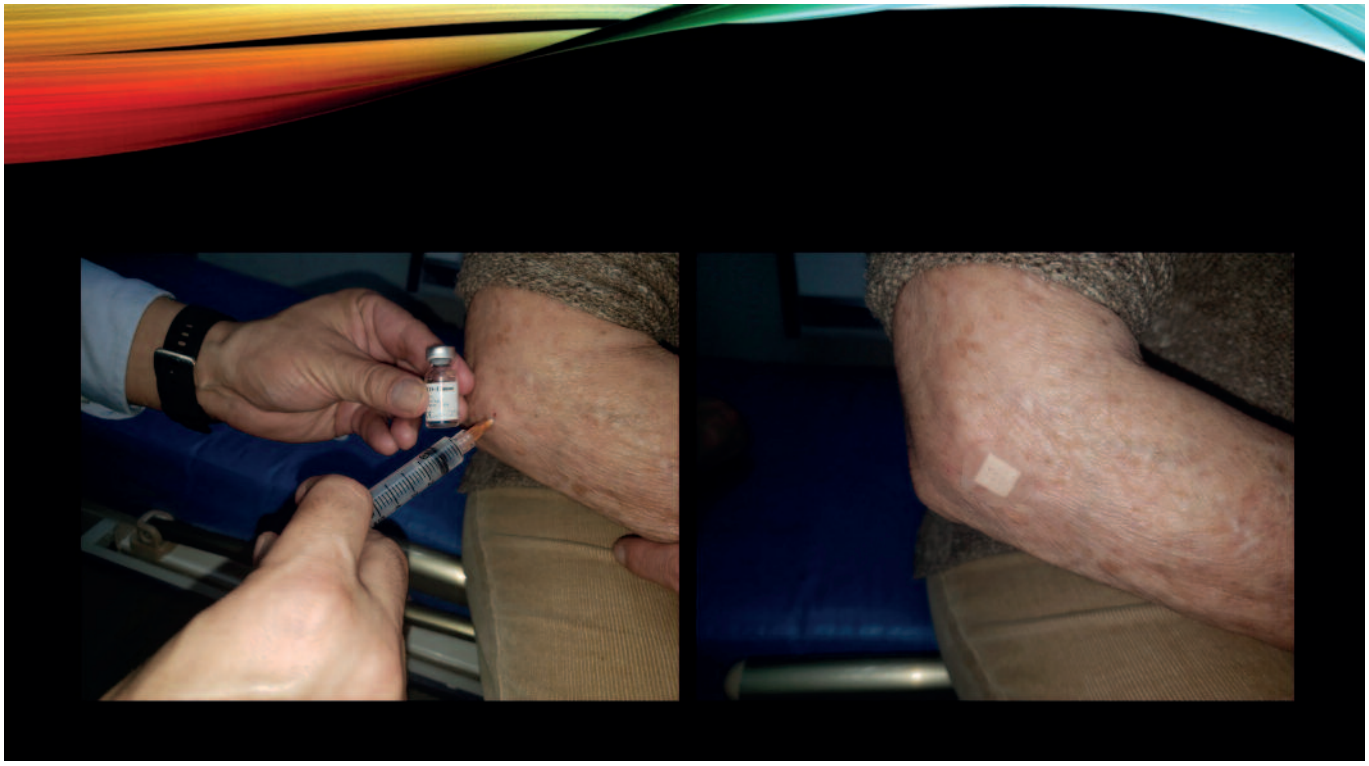
- ACTIVE PATIENTS
- DISCARDING OF PREVIOUS INEFFECTIVE TREATMENT
- MOST PEOPLE CHOOSE TO DO AN ULTRASOUND
- 98% RECOVERY RATE WHEN ADMINISTERING BETWEEN 4 AND 6 DOSAGES

PARTIAL RESULTS

- 15 PATIENTS TREATED FOR EPICONDYLITIS
- MOST PATIENTS ARE POLICEMEN
- 5 CIVILIANS
- 2 SPORTSPEOPLE

EPICONDYLITIS

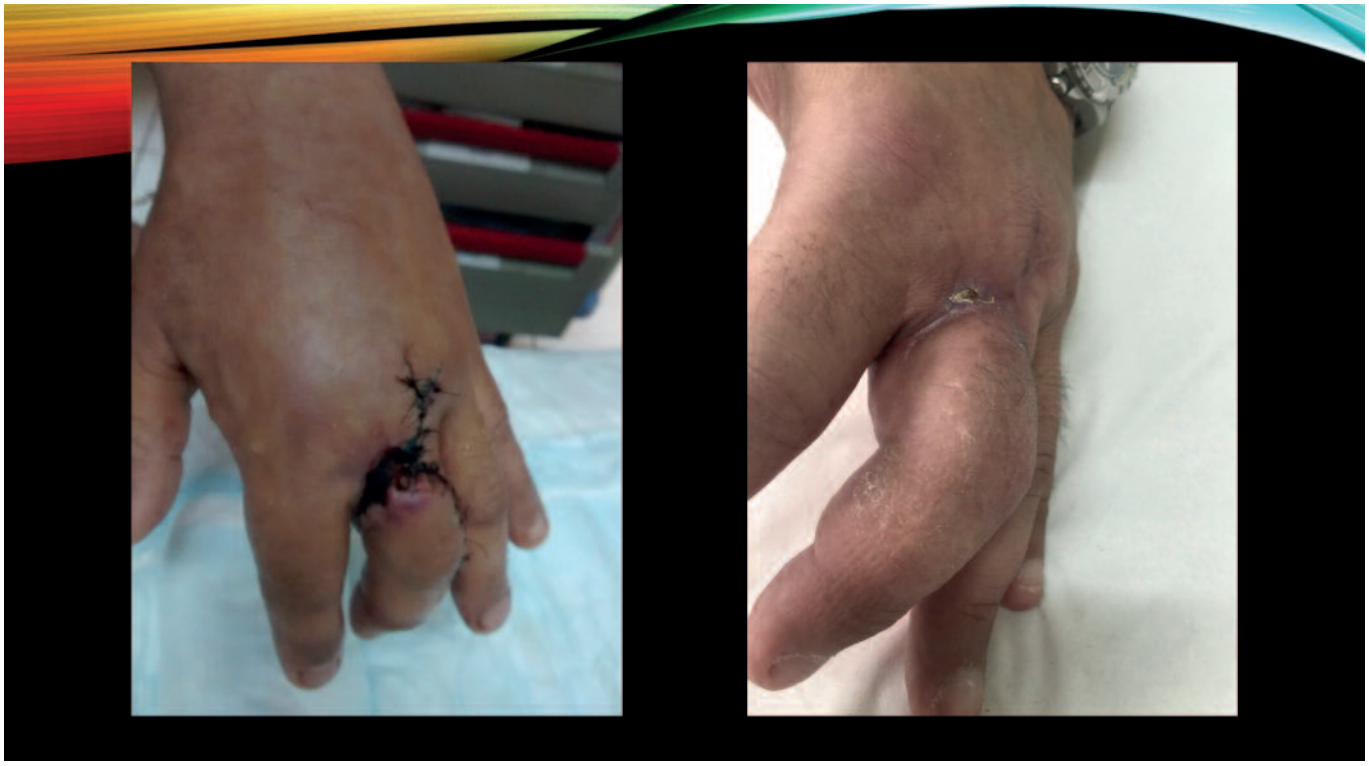
- 90% HEALED AFTER 2 MONTHS AND 6 SHOTS IN SIX MEETINGS
- INFILTRATIONS ACCORDING TO THE DIAGNOSE, PURE OR WITH DEGENERATIVE TISSUE INSIDE THE JOINT
- I PREFER THE USAGE OF MD-TISSUE

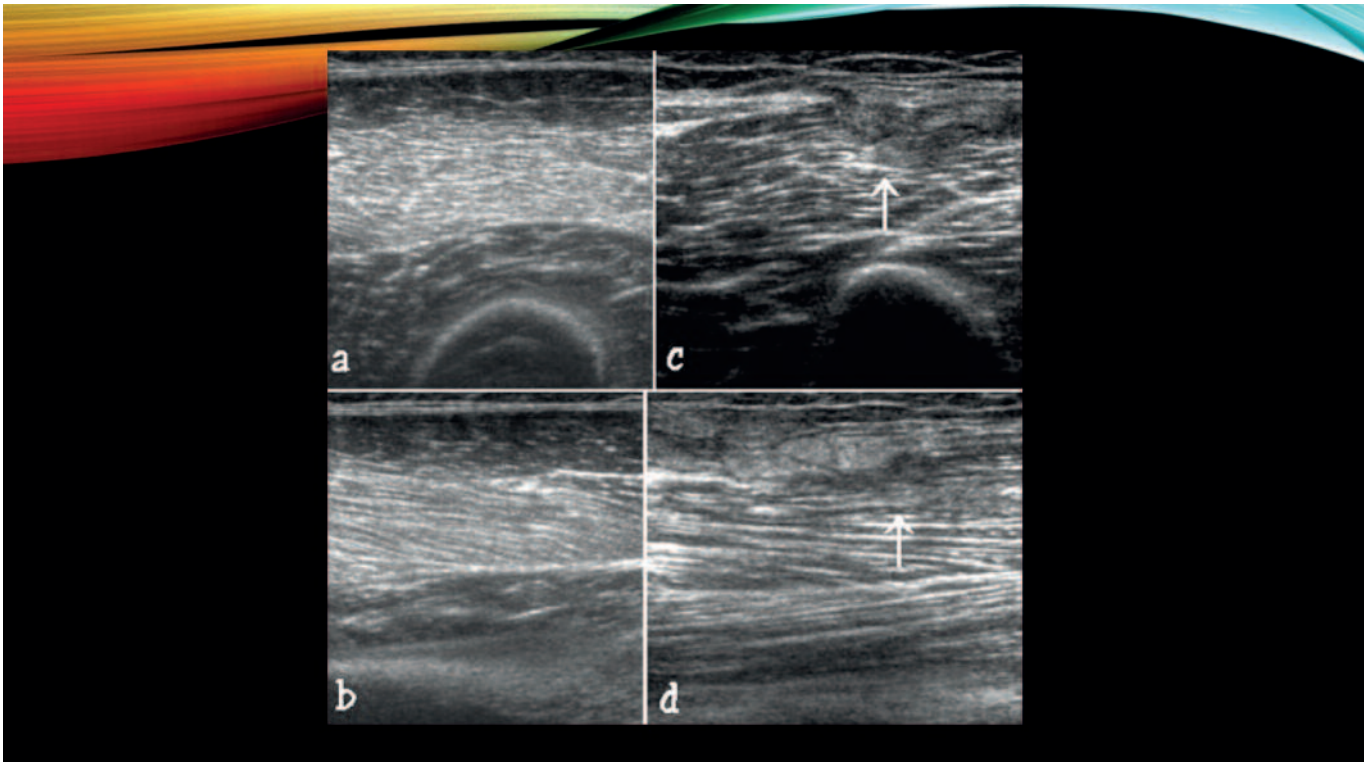


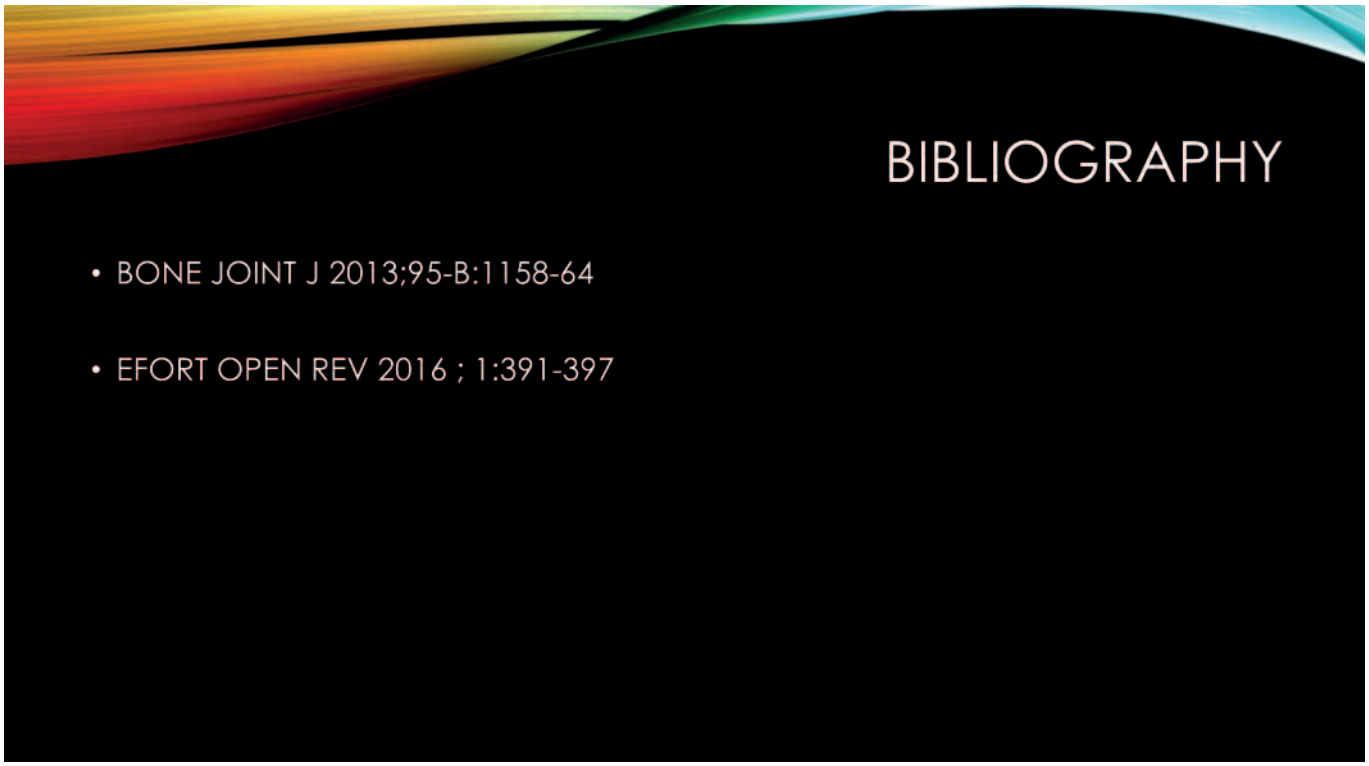
COLLAGEN MDs

I HAVE TREATED:

- ARTHRITIS
- TEARINGS
- TENDINITIS
- SPRAINS
- CARPAL TUNNEL SYNDROME
- TENOSYNOVITIS OF QUERVAIN
- SYNOVIAL CYSTS
- SCARS




a
c
b
d



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