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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 EPI-
CONDYLITIS, REFRACTORY TREATMENT,
SUBCUTANEOUS INJECTION, COLLAGEN,
PAIN, FUNCTIONALITY, DASH SCORE

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

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 tensile integrity, 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.

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.

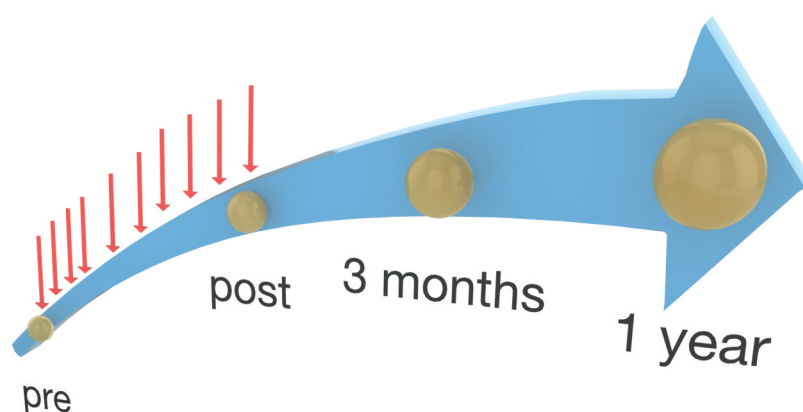


FIG. 1

Protocol.

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-

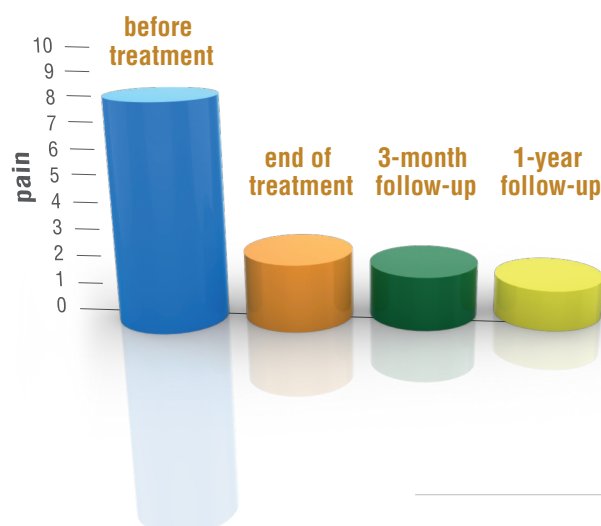


FIG. 2

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 inter-molecular 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-

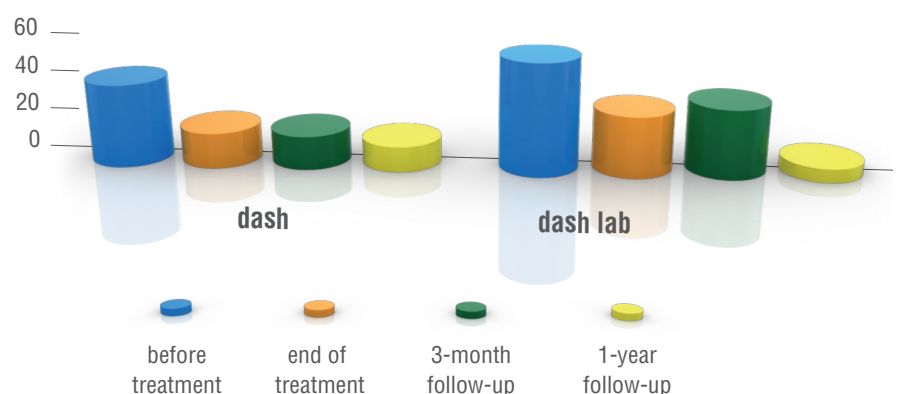


FIG. 3

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 effec-

tiveness 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 ob-

tained 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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