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ORIGINAL

Clostridium histolyticum collagenase (Xiapex®) in patients with peyronie disease. Expectations vs reality

Colagenasa clostridium histolyticum (xiapex®) en pacientes con enfermerdad peyronie. Expectativas vs realidad

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Abstract

Introduction: Peyronie's disease conditions the deformity of the penis. Its etiology and effective treatment to prevent surgery have not been determined. The approval of Xiapex®, collagenase from Clostridium histolyticum, generated great expectations.
Justification and objectives: Drug of recent use in Europe that requires multicenter studies to support its application. The aim is to collect the clinical results obtained from the implantation of Xiapex®.
Material and methods: A study of 24 patients treated with Xiapex® between 2017 and 2020 was carried out. Previous data was collected in consultation and information on the results by telephone questionnaire.
Results: The initial deviation was 61.4 degrees with a dorsal direction in 59%. 77% of the patients completed the 4 cycles. 41% reported having improved and would recommend the use of Xiapex®. 95% improved penile pain.
Discussion: Numerous studies have been published on Xiapex®. Many focus on modifying the treatment scheme proposed by the manufacturer, either by reducing the number of cycles or by the use of vacuum or traction devices. It is known that it is a disease with an important psychological profile, so it is necessary to consider the assessment of subjective results.
Conclusions: New studies are needed to collect and assess the real ability to modify the course of the disease with Xiapex®. It is necessary to insist on clear and concise inclusion and exclusion criteria, as well as a treatment scheme that achieves reproducible results.

Keywords: Peyronie, colagenasa, Xiapex, Clostridium, Histlyticum, curvature.

Resumen

Introducción: La Enfermedad de Peyronie condiciona la deformidad del pene. No se ha determinado su etiología ni tratamiento eficaz que evite la cirugía. La aprobación de Xiapex®, colagenasa de Clostridium histolyticum, generó grandes expectativas.
Justificación y objetivos: Fármaco de reciente uso en Europa que precisa de estudios multicéntricos que avalen su aplicación. Se busca recoger los resultados clínicos obtenidos de la implantación de Xiapex®.
Material y métodos: Se ha realizado un estudio de 24 pacientes tratados con Xiapex® entre 2017 y 2020. Los datos previos se recogieron en consulta y la información sobre los resultados mediante cuestionario telefónico.
Resultados: La desviación inicial fue de 61,4 grados con dirección dorsal en el 59%. El 77% de los pacientes completaron los 4 ciclos. El 41% refería haber mejorado y recomendaría el uso de Xiapex®. Un 95% mejoró del dolor peneano.
DISCUSIÓN: Han sido publicados numerosos estudios sobre Xiapex®. Muchos se centran en la modificación del esquema de tratamiento propuesto por el fabricante, bien por la disminución del número de ciclos o bien por el uso de dispositivos de vacío o tracción. Se sabe que se trata de una enfermedad con un importante perfil psicológico por lo que hay que considerar la valoración de los resultados subjetivos.
Conclusiones: Quedan muchos estudios por realizar que recojan y valoren la capacidad real de modificación del curso de la enfermedad con Xiapex®. Es necesario insistir en unos criterios de inclusión y exclusión claros y concisos, así como un esquema de tratamiento que consiga resultados reproductibles.

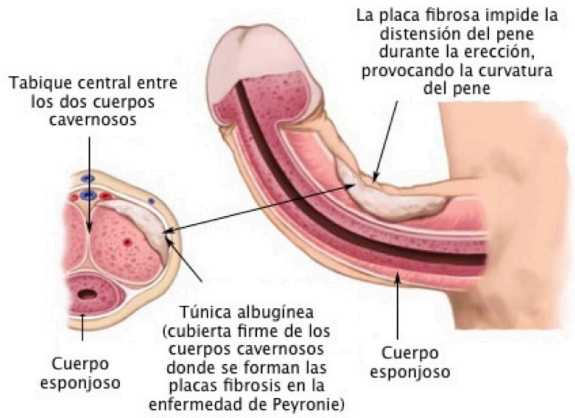
Palabras clave: Peyronie, colagenasa, Xiapex, Clostridium, Histlyticum, curvatura.

Introduction

Peyronie's disease is a disorder that causes the deformity of the penis, mainly, causing its curvature. However, it can lead to other results such as shortening, narrowing... In addition, it can associate other disorders or alterations such as erectile dysfunction.

Its etiology is not clearly defined and there are several theories for its justification. The most accepted, explains that it occurs as a result of a healing process that gives rise to the appearance of fibrotic plaques in the tunica albuginea of the penis. (**Figure 1**).

Figure 1: Image taken from https://www.mens-app.es/enfermedad-de-peyronie/.



The disease occurs in two phases. A first acute phase, which associates pain and in which penile curvature appears, followed by another chronic phase, which does not usually associate pain, in which the fibrotic plaque and curvature tend to stabilize.

For many years, urology has sought medical treatments that improve the patient's symptoms, penile curvature and deformity. However, good clinical results have not been achieved.

The European Medicines Agency approved in 2014 the use of collagenase from Clostridium histolyticum intraplaca (Xiapex®) for the treatment of adult men with Peyronie's disease, with a palpable plaque and curvature deformity of the penis of at least 30 degrees when start treatment.

As a last resort, surgical treatment continues. It is the one that achieves the greatest penile correction. The most used involve the plication of the tunica albuginea, the excision of the fibrous plaque, the application of incisions in them and, even, the implantation of penile prostheses to solve, in turn, the usually coexisting erectile dysfunction.

Justification and objectives

The arrival of Xiapex® was a motivation for urology, especially for andrological urologists who for many years had seen how patients who came to their consultations with this disorder could only offer not completely effective medical treatment or surgical treatment with the derived complications.

Treatment with collagenase from Clostridium histolyticum was already known for its use for Dupuytren's disease with palpable plaque. It is a disorder that results from a fibrotic process in the palmar fascia of unknown origin that causes progressive closure of the hand due to retraction of the superficial palmar aponeurosis.

The drug is composed of two collagenase enzymes whose coexpression and isolation is obtained from the anaerobic fermentation of a strain of the bacterium Clostridium histolyticum selected for its phenotypic characteristics. These collagenases, called AUX-I and AUX-II, are representative of the two main classes of collagenases produced by the germ.

Collagenases are proteinases that hydrolyze collagen, effectively cleave interstitial collagen such as that present in penile fibrotic plaques. Injection of Xiapex® into a Peyronie's plate can cause enzymatic rupture of the plate. After plaque rupture, penile curvature deformity and patient discomfort from Peyronie's disease are reduced.

Making a review of the current bibliography, there are no works that assess the application of this novel treatment in our closest environment. For this reason, we consider it essential to carry out a study that analyzes the clinical results obtained after the implantation of treatment with Xiapex®. The elements necessary to consider if the treatment with the collagenase injection has met the expectations generated after its approval for use will be evidenced or, on the contrary, if we find another non-surgical treatment whose efficacy is not always objective.

Materials and methods

This is a prospective study on patients who were candidates for treatment with Xiapex®. 24 patients were selected to undergo treatment with Clostridium histolyticum Xiapex® collagenase between January 2017 and March 2020. Of the total number of patients undergoing treatment, 2 of them refused to participate in the present study.

Initial clinical data and characteristics were collected in the consultation before initiating treatment with Clostridium histolyticum collagenase. The results related to the response to treatment were collected by telephone call to the patients since, in the context of a

Figure 2: Image taken from "Guía para el médico en el tratamiento de la Enfermedad de Peyronie con Xiapex".

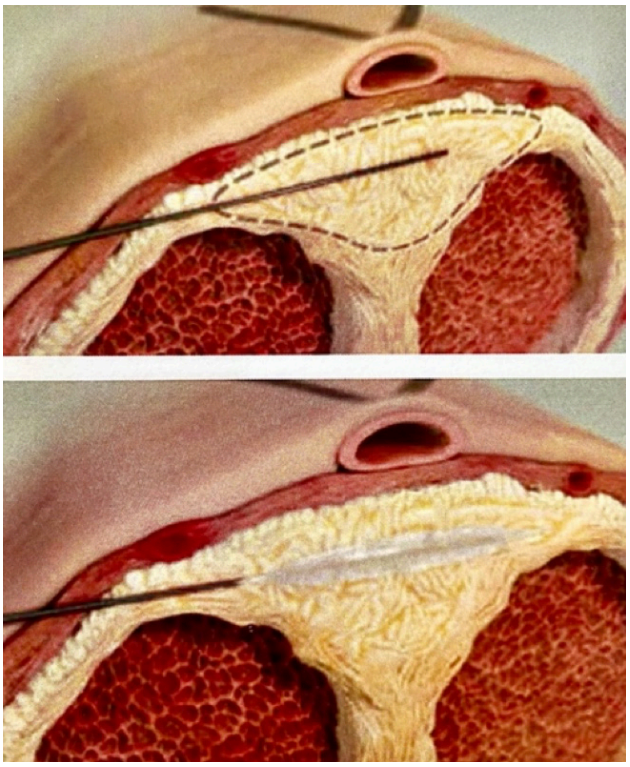
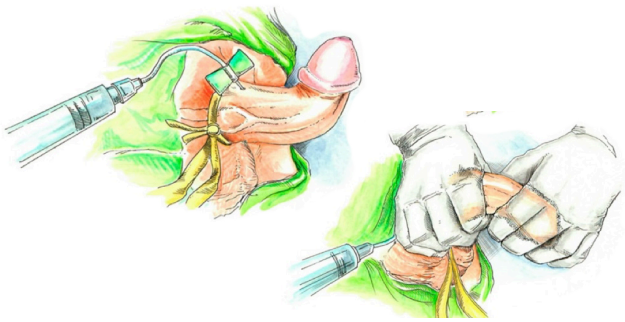


Figure 3: Image taken from "Guía para el médico en el tratamiento de la Enfermedad de Peyronie con Xiapex".

Figure 4: Modeling process. Image taken from https://tratamientopeyronie.com/fase-cronica/tratamiento-no-invasivo-inyectable/



COVID-19 pandemic, it was not possible to proceed to the appointment of the patients at the hospital center for the measurement and collection of results.

Initially, variables related to clinical aspects were analyzed, such as age at the onset of symptoms and at the beginning of treatment, risk factors (Diabetes Mellitus, arterial hypertension and vascular diseases) and if they had received previous medical treatment and what it had been. Likewise, variables related to the characteristics of the penis deformity were obtained, such as the angle of curvature, its direction, the length and width of the plate and, finally, whether they presented penile pain associated with the erection.

Regarding the information on the result of the treatment, collected through individualized telephone calls to the treated patients, questions were asked about general satisfaction with the treatment, reduction of the angle of curvature, modification of penile length, penile pain, if they would repeat the treatment and if would recommend it.

The application of the treatment was carried out following the indications that appear in the "Product Sheet", respecting the inclusion criteria: palpable plaque and curvature deformity of at least 30 degrees at the beginning of the treatment and less than 90 degrees. Patients with ventral deformity, "hourglass" or calcified plaque were excluded.

The complete treatment consists of applying 4 cycles. Each of them consists of 2 injections of the drug and an in-office penis modeling process. It should be between 1 to 3 days between the first injection and the second. Modeling is done 1 to 3 days after the second injection. The cycles should be approximately 6 weeks apart. In the time that elapses between one cycle and the next, the patient must perform penis modeling activities on a daily basis. (See **figure 2**, **3**)

Penis modeling is a manual procedure that helps reduce curvature deformity and straighten the shaft of the penis. In addition to this in-office penis modeling procedure, patients were instructed to perform penis modeling at home.

It can be administered up to a total of 4 treatment cycles, that is, 8 injections and 4 modeling procedures. A smaller number of cycles may be applied if the urology physician so indicates, if the patient refuses to continue with the treatment or, as indicated in the Technical Data Sheet, if the angle of the curvature after the first, second or third cycle is less 15 degree. (See **figure 4**).

Results

The treatment was applied in 22 male patients whose mean age was 59.3 years (range 39-73 years). Regarding

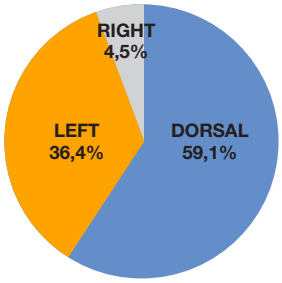
cardiovascular risk factors, 18,2% had Diabetes Mellitus (DM) and 27.3% had Arterial Hypertension (HT).

40.9% of the patients had previously received treatment with Auxin®, a drug that is used orally whose components are Vitamin A and E. In 4 of the patients who had received this treatment, other drugs such as Tamoxifen (3 cases) and Verapamil (1 case).

The time elapsed between the onset of symptoms related to Peyronie's disease and the start of treatment with Xiapex® was, on average, 1.2 years (range 0-3 years).

Regarding the clinical characteristics of the disease, the mean penile curvature angle was 61.4 degrees with a dorsal direction in 59.1% of the cases; in only 1 case there was curvature towards purely right laterality, the rest being to the left laterality. (See **figure 5**).

Figure 5. Direction angle curvature.



The mean length of the fibrotic plaque was 2.3 cm (range 0.5-4 cm) and the mean width was 1.2 cm (range 0.5-2.5 cm). 27.3% of the patients had pain before starting treatment.

In 77.27% of the patients, 4 treatment cycles were applied, that is, 8 injections of Xiapex®. In two cases, treatment could not be continued because patients did not continue to attend check-ups. In 1 case it was suspended due to not obtaining results and in another due to the appearance of another additional fibrotic plaque. Finally, treatment could not be continued in 1 case due to the European shortage of Xiapex®.

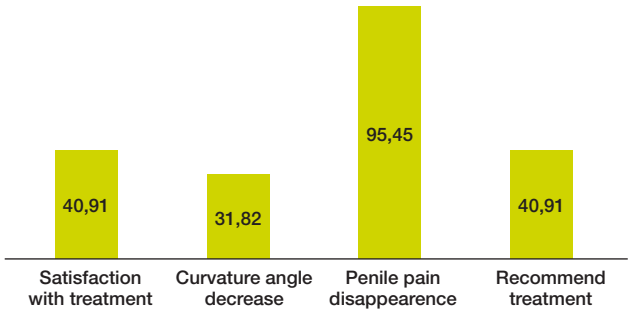
The evaluation of the results was carried out by means of a telephone call to the patients. 40.91% of them (9 patients) reported improvement after completing the treatment, and 31.82% (7 cases) indicated that they had perceived a decrease in the angle of penile curvature.

It is curious that 3 of the patients who claimed to have improved after treatment reported not having improved in the angle of curvature. This leads us to think that the improvement to which they referred was related to the disappearance of pain and the stabilization of the process, as well as to their overall psychological satisfaction.

On the other hand, one patient reported having noticed a decrease in the angle of curvature but, nevertheless, he considered that this fact alone did not improve his initial clinical situation.

Regarding penile pain, especially related to erection, 95.45% of the patients answered that it had disappeared. One of the main problems of penile curvature correction is penile shortening, 50% (11 cases) of the patients reported this fact. Finally, 40.91% of the patients would recommend Xiapex® treatment to other patients. (See **figure 6**).

Figure 6. Main variables taken from the telephone questionnaire (%).



As adverse reactions, only mention 1 case that presented severe but self-limited hematoma that did not require surgical drainage.

Discussion

Peyronie's disease has been studied for more than 260 years since François de la Peyronie described it in 1743. Despite this, epidemiological data that are currently available are limited. According to Chung et al1. the disease presents a prevalence rate between 0.4-20.3%, with a higher prevalence among patients with Diabetes Mellitus and erectile dysfunction. As can be seen, the range provided in the different studies is still very wide. In the USA, Stuntz et al[2]. (2016) carried out a survey in which 0.7% confirmed cases were determined compared to 11% of probable cases, which suggests that it is an underdiagnosed disease.

The age of onset of the disease is usually between 50-60 years, although more and more cases are reported in younger patients. In our study, the mean age coincides with that usually referred to, however, it can be stated that there are cases of younger patients, such as a 39-year-old patient who participated in the study.

The most commonly associated risk factors are diabetes, high blood pressure and vascular diseases, as can be seen in the results obtained in the present study.

In general, the first symptom usually referred to is penile deformity (52-94%) followed by penile pain (20-70%), as described in their study by Pryor[3] and Ralph[4]. The appearance of fibrotic plaques is reported as an initial symptom in 39% of patients with a dorsal deviation as the most frequent; as in the current study where it was present in 59% of the cases.

It is a disease with an important psychological affectation. Validated questionnaires and multiple studies, as reported by Nelson et al[5], show that around 50% of patients with Peyronie's disease have moderate or severe depression.

Classically, the management of the disease was based on the choice of surgical treatment over conservative treatment. Regarding the conservative, the studies are often contradictory and with very unsuccessful results. They mainly consisted of oral treatments such as pentoxifylline, vitamin E, tamoxifen, procarbazine, potassium paraminobenzoate (POTABA), among others.

One of the most used had been potassium para-aminobenzoate (POTABA); It is a drug with an anti-inflammatory and fibrinolytic effect due to the activation of monoamine oxidase. It was the only oral drug approved by the American drug agency for Peyronie's disease based on studies that concluded that, although it does not reduce penile curvature, it could prevent its progression.

Another option was colchicine, which could be given in combination with vitamin E. Colchicine is an alkaloid that inhibits the formation of microtubules and the secretion of collagen by fibroblasts. The second is an antioxidant with an effect on tissue regeneration. It was claimed that they could reduce pain, the size of the plaque and, in some cases, the degree of curvature.

Although, in routine medical practice a very insignificant effect was evidenced with these drugs. Even in the absence of adverse events, it was found that treatment with these could delay the approach to the disease in a more effective way.

Treatment with Xiapex® for all this was a before and after, it was not just another treatment option, it was the only non-surgical option that initially offered very promising results. Many centers, after being approved in Europe and despite the high economic cost involved, began to apply it to be able to offer patients with Peyronie's disease what was supposed to be an effective and non-surgical treatment.

The approval of this drug came after the IMPRESS I and II clinical trials. These are randomized, double-blind, placebo-controlled trials. Overall, a mean improvement in curvature of 34% was demonstrated compared to 18.2% in the placebo group. It was established that the greatest probability of improvement in curvature was in plaques curved between 30 and 60º, longer duration of the disease and absence of calcification. However, it is curious that 18.2% improved in the placebo arm.

One of the most controversial aspects has been the reference to the number of cycles. Many groups have studied the influence of the number of cycles on the results obtained. Anaissie et al6 in a retrospective review of 77 patients treated between April 2014 and March 2016 concludes that the therapeutic benefit decreases from the third cycle, not finding significant differences from this in the results obtained. In the same study, the researchers wanted to find predictive response factors, finding that only the response that the patient presents after the first cycle can serve to predict the final response. They consider that the 4-cycle protocol proposed in the product sheet is not being applied in most of the centers due to its high cost and difficulty in compliance with care. In most centers, alternative protocols are applied with fewer injections and adding traction mechanisms.

In the present study, the number of cycles indicated in the product sheet has been maintained. Although in some cases no significant improvement was observed after the application of the injections, the initial idea was maintained in order to be able to homogenize results and make a more objective comparison. Two patients who decided not to continue applying the treatment should be highlighted.

As mentioned above, in the period that elapses between cycle and cycle, penile modeling must be applied. This fact has also been questioned or valued in different studies. Ziegelmann et al[7] conducted a study in which 51 patients who completed the 4 cycles of collagenase treatments were analyzed and were divided into 2 groups: 35 patients underwent mechanical traction modeling and the rest without said device. No statistically significant differences were found in curvature reduction or penetration ability. Differences were reported, although with no degree of significance, in penis length, being + 0.4cm on average in the group that used the traction device. In the study by Raphl et al[4] include 2 groups in which a vacuum device is used with the difference that, in one of them, in addition, classical modeling is performed. It reports that there are no significant differences in the reduction of the angle of curvature. On the contrary, Fernández-Pascual et al[8] carry out a study in which they include 50 patients who undergo aggressive modeling and traction device and 94 patients to whom only aggressive modeling is applied. It concludes that the former achieve a 36% improvement in curvature compared to 28% for the latter. He adds that, in the first group, there is an increase in adverse effects such as ecchymosis, bruising and pain.

Another aspect to take into account is the overall satisfaction of the patient. In a study led by Ziegelmann et al9 from the Mayo Clinic in Minnesota analyzed in 69

patients treated with Xiapex®, among other things, the degree of subjective improvement. They conclude that patients reported a sensation of improvement in curvature with each cycle of collagenase injections. This study can be considered as the first to prospectively assess patient satisfaction not only with objective data but also subjective data provided by themselves with significant improvement in the ability to restore penetrative intercourse.

In the present study, up to 40% of the patients considered the treatment satisfactory, regardless of the reduction in the angle of curvature. Therefore, it must be valued that the assessment of this disease must be global, both in clinical objective aspects and in the patient's own experience. The implication of the psychological sphere cannot be forgotten and the evolution of the patient must also be considered in this area.

In relation to this issue, the study carried out by Anaissie et al[10] derives from the same conclusion. It also addresses the satisfaction of the partners, collecting a satisfaction of the patient and the partner of 67% and 71%, respectively. It establishes significant predictive factors of partner satisfaction such as previous sexual intercourse, the improvement in the ability to maintain relationships with the treatment and the absence of hypoesthesia in the glans after it. It therefore assumes that the injection of Xiapex® in patients with Peyronie's disease achieves a significant benefit for the sexual health of the couples.

With regard to safety problems and adverse effects, according to various studies, patients undergoing collagenase injections experience at least a mild or moderate reaction localized to the penis. Most frequently, according to Carson et al[11], is the appearance of hematoma (50.2%), penile pain (33.5%), inflammation (28.9%) and pain at the injection site (24.1%).

The analyzed patients presented mild reactions that were not specifically reported except for 1 case that presented penile hematoma and associated pain. In any case, they were all resolved spontaneously.

Analyzing the results globally, it can be considered that in our center the results were lower than those expected or those reflected in the literature. A possible cause could be a defect in the form in the application of the treatment but, probably, this should not be the main reason for this as it is a relatively simple technique, which does not require a long learning curve and has been carried out scrupulously following the indications given by the manufacturer.

However, the scientific method requires criticism and assessment of possible biases that may have occurred. The main one would be the low number of patients undergoing treatment. It is a generalized bias, already commented and pointed out in the vast majority of studies as in many of those previously referenced. Although this fact is understandable since it is a disease that, although it has a higher prevalence than what is really known, as previously indicated, the number of patients who consult for it is lower than the one who actually suffers from it in the population.

Another aspect that can skew the sample is the appropriate selection of patients. Although the inclusion criteria specified by the manufacturer have been followed, various studies have observed how there are factors that could influence the patient's response to treatment. These would be: plaque length, its calcification, long evolution time, among others. Although the mean time from the onset of symptoms to the use of treatment is 1 year, it could be, as supported by various studies, that the application in the acute phase, at the onset of symptoms, could favor the patient's response. The use of Doppler ultrasound should also be considered for an expanded study of the characteristics of the fibrosis plaque and to confirm the absence of calcification in the plaque.

Finally, another bias to be pointed out is the lack of validity of the questionnaire made to the patients to analyze the results obtained. This would have been more objective if the pertinent measurements and analyzes could have been carried out in a medical consultation with an adequate anamnesis and examination of the patients.

These aspects have also been valued in other works. Müller and Mulhall12 in a study based on another 26 published in the last 15 years on Peyronie's disease conclude that most of the published trials have lacked a control group and only a few have had any randomization, which constitutes a relevance bias. Even a consensus conference is considered necessary to share and establish guidelines for the definition, adequate duration of treatment and follow-up.

It can be considered that there are two aspects related to the treatment of the disease through the injection of collagenase that need further analysis and study. On the one hand, the placebo effect that the treatment has; As reflected in the studies that led to the approval of the drug, approximately 20% of those who were treated with placebo in the clinical trial presented significant improvement in the disease. This fact reveals an important psychological component in the disease, mentioned above, and, therefore, a questioning of the results collected in all the studies that address the treatment of Peyronie's disease. On the other hand, the fact that since December 31, 2019 the drug has been out of circulation in Europe is of special importance and significance. According to the American laboratory that produces it, it has decided to withdraw it from all over Europe for strictly economic reasons. Producing this drug is very expensive and the price in Europe is lower than in the US, being already high in our continent, assuming an outlay of between € 5000-7000 for 4

complete treatment cycles per patient. All of this can lead to questioning that it could be about more than price. Currently, there are drugs for benign diseases that involve a large financial outlay and that, nevertheless, remain available. Therefore, it can be deduced that the results initially reported in the studies cannot be extrapolated to those that most urologists assess in the patients they treat.

Other questionable considerations are the large number of studies that modify the initial protocol proposed by the manufacturer; some add traction or vacuum devices instead of the described modeling and others question the number of cycles. All this casts doubt on the very favorable result of the treatment of Peyronie's disease with Xiapex® collected in the literature.

Finally, as shown in most studies, the expectations created during the treatment approach to the patient take on special relevance in relation to the results that they assess. A clash between expectation versus reality that can further lead to frustration and psychological worsening of patients must be avoided.

It is important to know the difficulty that currently exists to present studies that start a path against the current, but it is a moral obligation to inform the scientific community of the results obtained in this study, with all the biases and objections mentioned, to collaborate in favor of medicine being able to continue advancing, and giving a reference to those centers that, like our case, the results obtained have not been as expected.

Conclusions

It can be concluded that treatment with Clostridium histolyticum collagenase is a safe and established treatment for Peyronie's disease. It seems that the evidence leads to think that it can affect the progression of the disease in the active phase, although there is an important placebo effect. It should also be taken into account that it is essential to associate a traction or modeling effect, intense and persistent over time, for which additional devices can be used.

The scientific evidence regarding the use of Xiapex® is extensive but variable, so it can be deduced that they are not easily reproducible.

There are multiple studies that report modified protocols, but they have a small number of patients and are largely uncontrolled. The results obtained are highly variable and depend on the selection criteria of the patients and multiple other predisposing factors that have not been fully clarified. Therefore, patients should be counseled on the efficacy of collagenase and the high cost of treatment. New clinical trials, with a better design, would be necessary to provide the drug with objective and reproducible results.

The withdrawal by the pharmaceutical company of the drug in Europe represents a burden to be able to advance in favor of greater scientific evidence and to achieve a non-surgical solution for patients affected by Peyronie's disease. We will have to wait for new studies, mainly from the US, to value the effectiveness of the product and demand, if necessary, its redistribution throughout our continent.

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