

INTRALESIONAL LOW DOSE METHYLPREDNISOLONE FOR THE TREATMENT OF ACTIVE PHASE PEYRONIE'S DISEASE: A SINGLE CENTER, PRELIMINARY PROSPECTIVE NON-RANDOMISED STUDY

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September 11, 2020

Abstract

Aim There are few types of drugs that can be used in the active phase of Peyronie's disease. Methylprednisolone is a corticosteroid with a strong anti-inflammatory effect. In this study, we aimed to evaluate the effect of intralesional low dose methylprednisolone treatment on patients in the active phase of Peyronie's disease. **Patients and Methods** Forty-eight patients suffering from Peyronie's disease active phase symptoms were included in the study. Methylprednisolone was administered intralesionally for 8 weeks, once per week, at a dose of 40 mg. The injection was applied into the plaques, which causes maximum curvature. Patients were evaluated before and after treatment for plaque size, angle of curvature, and erectile dysfunction according to the International Index of Erectile Function-5 and Peyronie's Disease Questionnaire. **Results** The mean age of the patients was 61.1 (43-78) years. Mean duration of the symptoms was 3.4 (0-9) months. The average plaque size before treatment was 13.6 mm (7.1-16.8) and after treatment, this value decreased to 10.8 mm (4.3-14.6) (p:0.025). The average scores of Peyronie's Disease Questionnaire elements; symptom severity, penile pain and bother/discomfort were 12.3, 19.1 and 6.2, respectively before the treatment. These scores were decreased to 8.9, 9.6 and 4.4, respectively after treatment. All subgroups of Peyronie's Disease Questionnaire scores were significantly improved after treatment (p:0.001, p<0.001, p:0.045, respectively). No adverse events were observed during or after treatment. **Conclusion** In order to recover the symptoms and signs, new and easily accessible drugs are required for use in the acute period of Peyronie's disease. In this context, treatment with intralesional low dose methylprednisolone in acute phase Peyronie's Disease is a promising and safe treatment option.

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Running Title: Methylprednisolone for treatment of Peyronie's disease

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Key Words: Peyronie’s disease; Methylprednisolone; Treatment

ABSTRACT

Aim

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Patients and Methods

Forty-eight patients suffering from Peyronie’s disease active phase symptoms were included in the study. Methylprednisolone was administered intralesionally for 8 weeks, once per week, at a dose of 40 mg. The injection was applied into the plaques, which causes maximum curvature. Patients were evaluated before and after treatment for plaque size, angle of curvature, and erectile dysfunction according to the International Index of Erectile Function-5 and Peyronie’s Disease Questionnaire.

Results

The mean age of the patients was 61.1 (43-78) years. Mean duration of the symptoms was 3.4 (0-9) months. The average plaque size before treatment was 13.6 mm (7.1-16.8) and after treatment, this value decreased to 10.8 mm (4.3-14.6) (p:0.025). The average scores of Peyronie’s Disease Questionnaire elements; symptom severity, penile pain and bother/discomfort were 12.3, 19.1 and 6.2, respectively before the treatment. These scores were decreased to 8.9, 9.6 and 4.4, respectively after treatment. All subgroups of Peyronie’s Disease Questionnaire scores were significantly improved after treatment (p:0.001, p<0.001, p:0.045, respectively). No adverse events were observed during or after treatment.

Conclusion

In order to recover the symptoms and signs, new and easily accessible drugs are required for use in the acute period of Peyronie’s disease. In this context, treatment with intralesional low dose methylprednisolone in acute phase Peyronie’s Disease is a promising and safe treatment option.

INTRODUCTION

Peyronie’s disease is a condition characterized by the formation of plaque due to collagen accumulation inside the tunica albuginea that surrounds the structures of the penile corpus cavernosum. This plaque can cause deformities such as penile shortening and curvature [1]. Penile pain and discomfort may occur during the active period of the disease, sexual functions are negatively affected, and erectile dysfunction may occur [2]. The incidence of Peyronie’s disease was found to be 3.2-8.9% [3]. Although young men are also affected occasionally, the disease is more common among older men—specifically, those over the age of 45—and its incidence increases with age [4].

Surgical treatment is not recommended in the active period of the disease. In this period, it is aimed to stop the formation of new plaques, avoid the plaque growth, to eliminate the pain. Approaches to treatment include the use of oral treatment agents and intralesional agents [5]. Oral therapies being used today include vitamin E, carnitine, colchicine, potassium amino benzoate, and phosphodiesterase type 5 inhibitors. However, none of these agents’ effectiveness has been fully proven [6].

Molecules such as corticosteroids, verapamil, interferon, and collagenase clostridium histolyticum are commonly used in intralesional therapy [5]. Among these, collagenase clostridium histolyticum stands out as the most effective agent, and there are many studies that have proven its effectiveness [1,7-9]. However, in some countries, this drug is difficult to obtain, and the cost of treatment protocols with this drug can be excessive. In addition, collagenase was withdrawn from the European market for commercial reasons.

Therefore, there is a search for more accessible treatment methods that can be used during Peyronie’s active period, especially in developing countries.

Methylprednisolone is a corticosteroid with a strong anti-inflammatory effect. It is used in the treatment of rheumatic diseases, acute/chronic inflammatory diseases, and allergic reactions [10]. It is a fairly inexpensive drug and easy to obtain. Since systemic and local side effects are also rare, it is probably that methylprednisolone could serve as an alternative treatment option in the acute period of Peyronie’s disease where inflammatory reactions are at the forefront [11].

The purpose of our study was to investigate the effectiveness and safety of intralesional methylprednisolone treatment in patients presenting in the acute period of Peyronie’s disease.

MATERIALS AND METHODS

Study Design

This is a prospective non-randomized preliminary study for observing the effectiveness and safety of using intralesional methylprednisolone to treat patients in the active phase of Peyronie’s disease. Patients who applied to our clinic for Peyronie’s disease and who were in the active phase of the disease between 2018 and 2020 were included in the study. To confirm that the disease was in the acute phase, we used the following criteria for inclusion: (1) less than 12 months passed since the onset of complaints; (2) absence of calcified plaque in penile duplex doppler ultrasound; (3) symptoms of painful erection; and (4) recent change in penile curvature. Patients who had completed the acute phase and progressed to the chronic phase disease stage, who had the presence of calcified plaque, who had prior medical or surgical treatment for Peyronie’s disease, who had a history of extra corporeal shock wave therapy (ESWT), who had hourglass and hinge deformity, and who were not sexually active were excluded from the study. Apart from hourglass and hinge deformity, patients with all types of curvature were included in the study.

Pre Treatment work-up

After erection was achieved by intracavernosal alprostadil injection, the maximum plaque size was measured before and after treatment by performing penile duplex doppler ultrasound in all patients. During the same procedure, the physician investigated whether there was calcified plaque. During erection, curvature angle was measured using a goniometer protractor. The point of injection was determined by marking the maximal curvature point, and the necessity of erection was eliminated before each procedure. To determine the point of maximum curvature, starting at the base of the penis, a straight line was drawn through the center of the straight portion of the penile shaft proximal and distal to the point of maximum curvature. The intersection of these lines was accepted as the maximal point of curvature, and the degree of curvature was determined by measuring the angle between these lines.

Before the first injection and one month after the last injection, all patients were assessed with Peyronie’s Disease Questionnaire (PDQ), consisting of 15 questions, and the International Index of Erectile Function (IIEF-5), consisting of 5 questions [12]. The score obtained from questions 1-6 of the PDQ questionnaire evaluates symptom severity (PDQS), questions 7-9 evaluate penile pain (PDQP), and questions 10-15 evaluate bother/discomfort symptoms (PDQB) [13].

Treatment Protocol

The treatment protocol was designed as an intralesional injection of 40 mg methylprednisolone to the maximum curvature point; this injection was repeated once a week for 8 weeks. No local anesthesia was performed before injection, but patients were allowed to use non-steroidal anti-inflammatory drugs and pain killers after injection. A 23G needle was used for injection. The dosage was 40 mg of the drug in its pure form (no dilution), which was loaded into a syringe and then inserted into the plaque at a right angle. The drug was then injected at different points of the plaque by slightly moving the needle around the injection point.

During the protocol, treatment was terminated and the patient was excluded from the study in cases of an unexpected side effects or worsening disease symptoms. All adverse events were recorded during the study

period. All procedures were performed by a single experienced urologist.

All patients voluntarily signed their consent to participate in the study. The study was approved by the Ethics Committee of Eskişehir Osmangazi University Faculty of Medicine.

Statistical Analysis

Statistical analysis was done with IBM SPSS V23.0 Software. No power analysis were performed. Continuous variables are reported as means, standart deviation and range. The Student's t test for unpaired data was used to compare means. Changes in plaque size, penile curvature, PDQ, and IIEF-5 scores from baseline to end of therapy were analyzed using ranked one-way analysis of variance (ANOVA). P values less than 0.05 were considered statistically significant.

RESULTS

Of the 61 patients who were admitted to our clinic for Peyronie's disease, 48 patients who met the inclusion criteria were included in the study. All patients completed the 8-week treatment protocol. No patients were excluded from the study because no serious side effects or worsening of symptoms were observed during the protocol. The mean age was 61.1 (43-78). The average time from the onset of complaints was 3.4 months (0-9). Curvature was dorsal in 19 (39.6%) patients, ventral in 5 (10.4%) patients, lateral in 12 (25%) patients, and dorsolateral in 12 (25%) patients. The average plaque size before treatment was 13.6 mm (7.1-16.8), and after treatment, this value decreased to 10.8 mm (4.3-14.6) ($p = 0.025$) (Figure 1). In 35 (72.9%) of the 48 patients, a decrease in plaque size was seen after treatment. Plaque size did not increase in for any of the patients after treatment. The mean curvature angle was 55.7 degrees (35-85) before treatment, whereas this value decreased to 52.5 degrees (33-85) after treatment. In 8 (16.7%) of the 48 patients, the curvature angle was reduced, but this decrease was not statistically significant ($p:0.07$) (Figure 2). In five patients (10.4%), curvature angle was increased. This increase was no more than 10 degrees. The changes in plaque size and curvature angle did not show any statistically significant difference with respect to curvature direction ($p = 0.145$). No local or systemic side effects or complications were observed during or after drug administration, excluding pain resulting from the injection of the drug.

The average IIEF-5 score before treatment was 18.1 (10-25). This score increased to 20.2 (10-25) after treatment. However, this rise was not statistically significant ($p = 0.069$). The PDQS score was 12.3 (4-18) on average, and this value decreased significantly to 8.9 (0-14) after treatment ($p = 0.001$). The PDQP score average was 19.1 (12-26) before treatment and significantly decreased to 9.6 (0-21) after treatment ($p < 0.001$). Finally, the PDQB score decreased significantly after treatment, as did the other scores. Before treatment, this value was 6.2 (4-12), and after treatment, it was 4.4 (2-10) ($p = 0.045$) (Figure 3).

DISCUSSION

Surgical treatment modalities of Peyronie's disease are continually being explored and increasing in diversity. However, surgical procedures can be performed only in the chronic phase of the disease [4]. In the acute phase in which inflammation is in progress, there are not many treatment methods with proven effectiveness [5]. Today, the most effective acute phase treatment is provided with collagenase clostridium histolyticum. This is the only treatment method licensed by the FDA. The effectiveness of Collagenase clostridium histolyticum has been proven by many recent studies [14–16]. However, especially in developing countries, using this agent can be very costly and the procurement of the drug can be difficult.

There are many studies about the etiology and physiopathology of Peyronie's disease in the literature. These studies generally focus on genetic, traumatic, and inflammatory processes [17–19]. However, regardless of the underlying cause, the inflammatory process that occurs later in the disease forms the basis of plaque formation. In the course of inflammation, Peyronie's disease occurs due to the production of inducible nitric oxide synthase (iNOS), which leads to an increase of nitric oxide and a corresponding increase in production of peroxynitrite anion. These processes result in the proliferation of fibroblasts and myo-fibroblasts and excessive production of collagen between the layers of the tunica albuginea, which is called penile plaque [20].

Corticosteroids are frequently considered to be an acute phase treatment modality of Peyronie’s disease due to their intense anti-inflammatory effects [21]. However, few studies have investigated the intralesional use of steroids. Of those that have, positive results were obtained with intralesional steroid use in terms of improving penile curvature angle, plaque size, and penile pain and discomfort during erection [22,23]. However, the use of these drugs has not become widespread, and this is largely due to the systemic side effects caused by the use of high doses of steroids and the local side effects that appear around the area of application. As far as we know, this study is the first research to consider low dose methylprednisolone in the treatment of Peyronie’s Disease. In our study, statistically significant improvements were found for this treatment, especially in plaque size, severity of symptoms, and penile pain and discomfort during erection. We believe that the use of the drug in a low dose of 40 mg and with one-week intervals between injections would prevent the expected complications of steroids.

PDQ is a questionnaire that has been used many times to investigate the effectiveness of treatment methods used in Peyronie’s disease. Its reliability and effectiveness have been proven [24,25]. It is a scale that assesses the patient’s perspective on the disease, not just in the physical sense, but also in the psychosexual perception. It was observed that the complaint of pain—one of the typical findings of Peyronie’s disease, which disturbs the patient and occurs during erection—decreased significantly after methylprednisolone treatment. Naturally, the sexual performance of patients will improve with the reduction of this complaint. Our study showed an increase in IIEF-5 scores after treatment; however, this increase was not statistically significant. This may be due to the low number of patients in our study. Another reason could be that basal IIEF-5 values are already high, so there may be no significant increase after treatment.

Study Limitations

The main limitation of the current study was the low number of patients. Additionally, it is not a placebo-controlled randomized study. However, we believe that the results obtained from our study are likely to be replicated in comprehensive double-blind randomized placebo-controlled studies that should be done in the future. One of the methodological limitations was the preferred method of plaque size measuring. Using ultrasound for measuring the plaque size is easy but not reliable because the variable and subjective measurement depends on the person who performs the ultrasound. In order to minimize this subjectivity, all ultrasound procedures were performed by same clinician. Finally, the short follow up time after treatment protocol negatively affected the expected change in IIEF scores because IIEF is made to evaluate erectile function in the past six months.

Conclusion

The etiology of Peyronie’s disease has not been fully elucidated, but the inflammatory process has an important place in the disease’s physiopathology. The fact that the only drug that is licensed for the acute phase of the disease is collagenase clostridium histolyticum, and that the effectiveness of other previously-attempted methods has not been fully proven, makes us predict that new treatment modalities will be investigated in the future as well. Our study shows that intralesional usage of low dose methylprednisolone is effective for improving symptoms and signs during the active period of Peyronie’s disease. Thus, it may lead to a more progressive transition of the disease from the acute phase to the chronic phase, resulting in less penile deformity and less subsequent complicated correctional surgeries for affected patients.

DISCLOSURE STATEMENT

Authors declare no conflict of interest

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Table 1. Characteristics of the patients.

	Mean	Min	Max	SD (\pm)
Age	61.1	43	78	11.8
Disease duration (months)	3.4	0	9	2.3
Baseline curvature ($^{\circ}$)	55.7	35	85	24.3
Baseline plaque size (mm)	13.6	7.1	16.8	3.7

Table 2. Baseline values according to direction of the curvature.

	Dorsal (n:19)	Ventral (n:5)	Lateral (n:12)	Dorsolateral (n:12)	p
Age (mean \pm SD)	63.3 \pm 12.1	53.2 \pm 5.4	65.3 \pm 7.8	56.9 \pm 11.1	0.135
Plaque Size (mm) (mean \pm SD)	11.9 \pm 3.1	15.6 \pm 1.2	15.9 \pm 2.4	13.3 \pm 2.3	0.065
Angle of Curvature ($^{\circ}$) (mean \pm SD)	50.4 \pm 12.9	62 \pm 8.4	54.5 \pm 10.1	62.7 \pm 20.5	0.045

Figure Legends

Figure 1. Improvement in plaque size after treatment.

Figure 2. Improvement in curvature angle after treatment.

Figure 3. Changes in questionnaire scores after treatment. IIEF-5: Five question version of International Index of Erectile Dysfunction; PDQS: Peyronie’s Disease Questionnaire Symptom Severity; PDQP: Peyronie’s Disease Questionnaire Penile Pain; PDQB: Peyronie’s Disease Questionnaire Bother/Discomfort.



