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Original Research Article

The study of short-term efficacy of intralesional injection of combination of triamcinalone, hyaluronidase and mitomycin in Peyronies disease

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ABSTRACT

Background: Peyronies disease (PD) is physiologically and psychologically devastating disorder that is manifest by a fibrous inelastic scar of tunica albugenia resulting in palpable penile scar and deformity. Different modalities of nonsurgical treatment options exist without promising results in the long-term improvements of symptoms. The injection of pharmacologically active agents directly in to the penile plaque results in localized delivery and higher drug concentrations inside the plaque. With this rationale the study is planned to analyze the effectiveness of intralesional injection of triamcinalone, hyaluronidase, and mitomycin in the treatment of PD.
Methods: Patients with symptomatic PD presenting at PGIMER from 1st July 2013 to 30th September 2014 were included in the study after obtaining the informed consent. A freshly prepared solution of a mixture of Triamcinalone, Hyaluronidase and Mitomycin was injected at the periphery as well as in the plaque. The patients were followed up for every four weeks for three months for the improvement of symptoms.
Results: A total of 21 patients of symptomatic Peyronies disease with mean age of 44.4 and mean duration of 5.6 months were treated and followed up at PGIMER during July 2012 to September 30th, 2014. After completion of 3 months of treatment, 15/21 patients showed improvement in penile curvature. The overall response rate was 71.4% (p=0.001). 14/21 patients showed improvement in plaque size. The overall response rate was 66.66 (p=0.036). The IIEF-15 and PROSB score improved significantly both at 1st and 3rd month of follow up from the baseline score.
Conclusions: This pilot study showed that the intralesional injection therapy is safe, well tolerated and effective in reducing the plaque size, penile curvature, and erectile dysfunction and patient's bothersome score.

Keywords: International index of erectile function 15 (IIEF15), Patient reported outcome and bothersome (PROB) score, Peyronies disease (PD)

INTRODUCTION

Peyronies disease (PD) is physiologically and psychologically devastating disorder that is manifest by a fibrous inelastic scar of tunica albugenia resulting in palpable penile scar in the flaccid condition and causing penile deformity including penile curvature, indentation, hourglass shape and buckling erection, hinging, narrowing shortening and painful penile erections.[1]

The etiology of PD is unknown, however an insult (repetitive micro vascular injury or trauma) to the tunica albugenia is the widely accepted hypothesis.[2] PD starts with an acute inflammatory process, and this is

characterized by increased proliferation of tunica fibroblasts, some of which differentiate in to myofibroblasts with excessive deposition of collagen the persistence of fibrin and elastin fragmentation. The most commonly associated co-morbidities are diabetes, hypertension, lipid abnormalities, ischemic cardiomyopathy, erectile dysfunction, smoking and excessive consumption of alcohol. Duputyrins contracture is more common in patients with PD. Forceful penetration and penile trauma have long been thought to be causative factors.[3] More contemporary thinking would consider PD as a disorder of wound healing and as such maybe considered to the formation of hypertrophic scar.[4]

Different modalities of treatment are used for management of PD. Medication given orally is often the first choice of therapy at the early stage of disease especially when sexual activity is not severely impaired.[5,6] Vitamin E, pentoxyphyllin, acetyl esters of carnitine, colchicines, potassium paraaminobenzoate, tamoxifen have been used with variable success rates but their value remains questionable.[7] Injection of drugs at plaque is an alternate non-surgical treatment. The injection of pharmacologically active agents directly in to the penile plaque results in localized delivery and higher drug concentrations inside the plaque. Intralesional steroids are long in use which is thought to act by opposing the inflammatory milieu responsible for peyronies plaque progression via inhibition of phospholipase A2 and suppression of immune response and by decreasing collagen synthesis. Mitomycin-C (MMC) inhibits fibroblast proliferation and is effective in preventing scar formation; hyaluronidase is the major enzyme responsible for lysis of the scar and had found utility in various dermatological procedures, no study has been done by combining all the 3 drugs in a single mixture. since all the 3 drugs acts at different levels of fibrous plaque formation and intralesional therapy achieves highest local drug concentration and administration of this drug mixture probably gives better results in symptoms of PD. With this rationale and with the belief that PD is essentially a disease of hypertrophied scar, authors planned this study to analyze the effectiveness of intralesional injection of triamcinalone, hyaluronidase, and mitomycin in the treatment of PD.

METHODS

Patients with symptomatic PD presenting at PGIMER from 1st July 2013 to 30th September 2014 were included in the study. The patients were explained in detail about the pilot study and a written informed consent was obtained. A detailed history was recorded. It included the patient interview history focusing on onset and duration of symptoms. The detailed past medical and sexual history was evaluated. Medical history was focused on personal or family history of wound healing disorders including duputyrins contracture. Risk factors for ED such as dyslipidemia atherosclerotic disease, history of tobacco use and diabetes was asked and recorded. ED was assessed by IIEF-15 questionnaire. Based on this, ED was further categorized in to mild, moderate and severe types of ED. Patient reported outcome and symptom bother score was also recorded. Physical examination focused on genital examination, measurement of penile length, penile curvature location of the plaque was assessed. Penile plaque was detected by doing ultrasonography of penis using a high frequency probe. X-ray of stretched penis in oblique view was done to assess the position of calcification. Routine blood work up along with work up for ED like FBS/lipid profile/hormonal profile was done. A freshly prepared solution of a mixture of 2ml lidocaine, 2ml triamcinalone (40mg/ml), 1ml hyaluronidase (1500IU), and 1ml of mitomycin (0.2mg) was injected at the periphery as well as in the plaque via 10ml syringe and 25G/26G needle.

It is proven that the drugs used in the study can be mixed without any harm and doesn't alter the potency of each drug. Approximately 24 to 72hrs of injection patients were underwent an investigator penile plaque modeling. Using the plaque as the fulcrum point, the investigator applied the firm, steady pressure to elongate the penis, the penis was held in this position for 30 seconds, the procedure is repeated for 3 times twice per month and subjects were instructed to perform standardized home penile modeling 3 times daily. Subjects were also advised to make a gentle attempt to straighten the penis without pain during spontaneous erection. Follow up was done at 4weekly intervals for a period of three months. At each follow-up visit, patients were assessed for the improvements in ED and bother scores, their penile curvature and the plaque characteristics. Patients were given two injections at one monthly interval i.e. they received 2 more injections after the first injections.

Statistical analysis

Descriptive estimates were calculated as mean, median and standard deviation. Frequencies and proportions were calculated for qualitative variables. Chi square test of independence (with Fisher exact test if required) was used to see association of intervention groups with various categorical variables. $p<0.05$ was taken as significant.

RESULTS

A total of 21 patients of symptomatic peyronies disease with mean age of 44.4 and mean duration of 5.6 months were treated and followed up at PGIMER during July 2012 to September 30th, 2014.

Associated abnormalities

Diabetes was seen in 12 patients (57.1%), tobacco consumption in 13 patients (61.9%), deranged lipid parameters was seen in 8 patients (38%), low serum testosterone levels was seen in 7 patients (33.33%) and 1

patient had penile trauma leading to development of penile plaque. Thus, majority had one or other factors responsible for endothelial dysfunction.

Peyronies disease specific baseline characteristics

The penile plaque and curvature were seen all the patients of the study but penile pain during erection in association with plaque and curvature was seen in 17 patients (81%) while rest didn't have pain during erection.

Penile plaque

The most common location of penile plaque was Dorsal, which was seen in 16 patients (76.2%). The other locations of the plaque were dorso-ventral in 2 patients (9.5%), right- lateral in 2 patients (9.5%) and Ventral in 1 patient (4.8%). The size of the penile plaque was categorized in to 3 groups as, <1cms, 1-2 cm, and >2cm. 13 patients (61.9%) had baseline penile plaque size of 1-2cms, 8 patients (38.1%) had baseline plaque size of >2cms, none of them had baseline plaque size of <1cm.

Penile curvature

The penile curvature was categorized in to 3 groups of <300, 30-600, and >600. 9 patients (42.9%) had baseline curvature of <300, 10 patients (47.6%) had curvature of 30-600 and 2 patients had baseline curvature of >600.

Patient reported outcome and symptom bother score (PROSB)

The mean baseline PROSB score was 26.1 with a range of 1 to 48.

IIEF-15 score

The baseline mean IIEF score was 39.9 with a range of 23 to 54.

Change in parameters after 3 months of treatment

All patients received 3 injections of trimix as per protocol 1 month after last injection patients were reevaluated at 1 month and 3 months after the inclusion.

Penile plaque

After 3 months of treatment, 14/21 patients showed improvement in plaque size. The overall response rate was 66.66% this was statistically significant (p=0.036).

On subgroup analysis 8/13 patients (61.5%) with plaque size of 1-2cm showed reduction to <1cms, 6/8 patients with plaque size of >2cm showed improvement, of these 6 patients 1 patient had plaque size of <1cms and rest 5 had size 1-2cm.

Table 1: Crosstab comparison of baseline penile plaque size and penile plaque size after 3 months of completion of treatment.

Baseline plaque size	<1cm	1-2cm	>2cm	Total
1-2cm	8 (61.5%)	5	0	13
>2cm	1 (12.5%)	5 (62.5%)	2	8
Total	9	10	2	21

Penile curvature

After completion of 3 months of treatment, 15/21 patients showed improvement in penile curvature. The overall response rate was 71.4%, this was statistically significant (p=0.001). On subgroup analysis 4/9 (44.4%) with penile curvature of <300 showed complete improvement in penile curvature, 9/10 (90%) patients with penile curvature of 30-600 reduction in curvature to <300 and all the patients with curvature of >600 showed reduction to 30-600.

Table 2: Crosstab comparison of baseline penile curvature and penile curvature after 3 months completion of treatment.

Baseline penile curvature	<30°	30-60°	>60°	No curvature	Total
<30°	5	0	0	4 (44.4%)	9
30-60°	9 (90%)	1	0	0	10
>60°	0	2 (100%)	0	0	2
No curvature	0	0	0	0	0
Total	14	3	0	4	21

The PROSB score and IIEF-15 score

There was a significant change in IIEF15 and PROSB score at 1st month and 3rd month of follow up from baseline PROSB score.

Adverse effects

Procedural pain was the most common adverse effect. It was seen in 66.67% (n=14) at the 1st injection which decreased to 42.8%(n=9) during 2nd injection and 19% (n=4) in 3rd injection. Local erythema and induration

were reported in 1 case during 2nd injection which was relieved with oral analgesics and anti-inflammatory agents and 1 patient during 2nd injection developed. Penile ulcer of 1*1 cm size over injection site which was managed by local debridement wound closure.

Table 3: Adverse effects.

Adverse effects	1st injection	2nd injection	3rd injection	Treatment given
Procedural pain	14 (66.7%)	9 (42.8%)	4 (19%)	Spontaneously relieved
Local erythema and induration	1 (4.8%)	Nil	Nil	Oral analgesics and anti-inflammatory agents
Injection site ulceration	Nil	1 (4.8%)	Nil	Local debridement and wound closure
No adverse effects	6 (28.6%)	11 (52.4%)	17 (81%)	NA

DISCUSSION

Peyronies disease (PD) is often physically and psychologically devastating for patients, and the goal of treatment is to improve symptoms and sexual function without adding treatment-related morbidity.[8,9] The potential for treatment-related morbidity following more invasive interventions, such as surgery, creates a need for effective minimally invasive treatments.[9]

Most available minimally invasive treatments lack critical support for effectiveness due to the absence of randomized, placebo-controlled trials (RCTs) or non-significant results.[8]

Peyronies disease is essentially a disease of hypertrophied scar and several studies have explored the utility of agents which are effective against scar like steroids, hyaluronidase, mitomycin, collagenase. These agents hold score promise for this poorly understood and yet devastating disease.

The triamcinolone decreases the inflammatory milieu at the fibrous plaque, hyaluronidase inhibits the TGF-b and collagen deposition at the plaque site, and mitomycin inhibits the fibroblast proliferation at the plaque site.[10,11] Since all the 3 drugs acts at different levels of fibrous plaque formation and intralesional therapy achieves highest local drug concentration and administration of this drug mixture probably gives better results in symptoms of PD.

Lamprakopoulos et al, did a study in a year 2000 with Betamethasone, hyaluronidase and lidocaine. But no study has been conducted with mixture of Triamcinolone, Mitomycin, and Hyaluroniodase.[10]

Authors planned this pilot study to analyze the effectiveness of intralesional injection of triamcinolone, hyaluronidase, and mitomycin in the treatment of PD.

This pilot study included 21 patients of symptomatic peyronies disease with mean age of 44.48 and mean duration symptoms of 5.6 months. Penile plaque and curvature was seen in all 21 patients, penile pain during erection was seen in 17 patients (80.95%) in contrast to William et al where penile pain during erection was seen in 27%, penile curvature in 49%, and a palpable plaque in 39% of the patients of PD.[12]

The Peyronies disease has been reported to be associated with Erectile dysfunction (ED), clinical depression, diabetes, hypertension, dyslipidemia, low testosterone, obesity, smoking, and duputyrins contractures.[12]

In present study majority of them had diabetes and tobacco consumption, one third of them had low serum testosterone levels, one patient was obese, and another patient had penile trauma leading to development of penile plaque.

The most common location of plaque was dorsal. After 3 intralesional injection therapy the overall response rate was 66.66%, and 61.5% patients showed improvement in plaque size from 1-2cm group to <1cm, and 62.5% of patients showed improvement in plaque size from >2cm to 1-2cm group. These improvements were statistically significant. This is in contrast to Lamprakopoulos et al, study in which 112 men were given mixture of Betamethasone, hyaluronidase, and lidocaine.[12] The plaque size in the study was categorized in to <1cm, 1-2cm and >2cm. A total of 12 such injections were given. The overall response rate was 86%, complete cure rate was 31% and improvement was noted in 55% of patients. However, in lamprakopoulos study the penile curvature, IIEF score and PROSB score were not assessed.

The penile curvature in present study was categorized in to <30°, 30-60° and >60° group. After 3 months of intralesional therapy the overall response rate was 71.4% (15 out of 21) which was statistically significant. On subgroup analysis, 90% of patients showed improvement in curvature from 30-60° group with decrease in curvature from 30-60° to <30°, all the patients in >60° group showed improvement in curvature with decrease in curvature from >60° to 30-60° whereas 4 out of 9 patients showed complete improvement in curvature in <30° group with p value of (p=0.001).

A study by Gelbard et al, with intralesional injection of purified CCH where 31 men who were grouped according to penile curvature as <30°, 30-60° group and >60° group.[13] After 3 months of treatment 100% improvement seen in <30° group, 36% improvement in 30-60° group and 13% improvement in >60° group. Although authors did not find such a high success rate in patients with <30° curvature group, but more patients with severe curvature (30°-60° and > 60°) showed improvements than in the above-mentioned study.

Patient reported outcome and symptom bother score (PROSB) in each visit, showed a significant improvement at 1st month and 3rd month of follow up from baseline PROSB score ($p<0.05$) indicating that the patients were happy and comfortable during the treatment and their bother decreased with each follow-up. The baselines mean PROSB score was 26.5, after 1 month of treatment the mean PROSB score was 15.4 and after the 3 months it decreased to 13.05. this is in accordance to the study by Gelbard et al, study with intralesional injection of CCH in 553 patients of symptomatic Peyronies disease, the response to treatment after 3 months was assessed using the bother score with p value of ($p=0.0453$).[13]

The IIEF-15 questionnaire was asked to detect ED at each follow up and IIEF score was noted. The baseline mean IIEF score was 39.9, in the 1st month it improved to 41.1 and after 3 months of treatment the score was 42.5. IIEF-15 score was improved significantly both at 1st and 3rd month of follow up from the baseline IIFE-15 score ($p=0.003$). The Trimix is well tolerated and shows significant improvement in all factors associated with peyronies disease even in a shorter follow-up.

The limitations of the study were as this pilot study was done with small number of patients with short duration of follow up and without any comparative arm and blinding.

CONCLUSION

This pilot study showed that mixture of triamcinolone hyaluronidase and mitomycin is safe, well tolerated and effective in reducing the plaque size, penile curvature, and erectile dysfunction and patient's bothersome score due to disease over a short course and short-term follow-up. However, to draw stronger conclusions studies including a larger number of patients and longer follow-up is warranted.

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