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Progression of Peyronie's Disease during Tamoxifen Treatment

Jinwook Kim[1], Tae Il Rho, Tae Yong Park, Soon Tae Ahn, Mi Mi Oh, Du Geon Moon

Department of Urology, Korea University Guro Hospital, Seoul, Korea

= Abstract =

Purpose: Medical treatment of Peyronie's disease with tamoxifen has been initially proposed as acting upon the early phase of the disease. As recent reports show no significant benefit of tamoxifen, we review the long term results of tamoxifen treatment of Peyronie's disease.

Materials and Methods: Time to progression during tamoxifen treatment of patients showing acute disease and chronic disease was compared. The acute phase was identified by pain during erection. Progression was defined as enlargement of plaque size or appearance of calcification.

Results: The average treatment duration was 15.9±13.8 months (range: 3 to 48 months). The median time to progression was 7 months for acute patients and 20 months for chronic patients. Eighty percent of patients in the acute phase showed relief of pain; however, overall progression was 72.1% (78.0% for acute, 66.7% for chronic). Patient history, comorbidities, serum testosterone or initial plaque characteristics, and severity of curvature were not predictive of disease progression.

Conclusions: Tamoxifen showed no significant benefit in slowing the progression of Peyronie's disease in the acute phase over the chronic phase. Peyronie's disease continued to progress, though at a dampened rate for patient's in the chronic phase.

Key Words: Peyronie's disease, Tamoxifen, Medication

Introduction

Peyronie's disease is a progressive inflammatory condition involving the tunica albuginea of the penis. Current epidemiologic estimates of the prevalence range from 3.2% to 8.9%, usually affecting men between 40 and 70 years of age.[1,2] Current recommendations suggest medical treatment for early phase disease, which is characterized by progressive deformity and painful erections.[3,4] However, due to the lack of clear understanding of the etiology, a plethora of treatment alternatives have been suggested.

Tamoxifen was introduced as a nonsurgical option in 1992 by Ralph et al[5] based on its suggested role in the overproduction of transforming growth factor -beta (TGF-β) in fibroblasts of the early inflammatory phase.[6] Nearly two decades since its introduction, current views are skeptical of its further use.[7] A nationwide study performed in the US showed that currently only 1% of urologists use tamoxifen as a first line treatment.[8]

Considering that tamoxifen was intended for the inflammatory acute phase of Peyronie's disease, we hypothesized that its use would either delay or abate its

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Correspondence to: **Du Geon Moon**
Department of Urology, Korea University Guro Hospital, 97 Gurodong-gil, Guro-gu, Seoul 152-703, Korea
Tel: 02-2626-1310, Fax: 02-2626-1321
E-mail: dgmoon@korea.ac.kr

progression. The current study retrospectively reviews patient treatment outcomes to compare the effects of tamoxifen on overtly acute presentations with painful erections and stable forms of Peyronie's disease, thus providing an estimate of delay in progression that treatment has provided.

Materials and Methods

We restrospectively reviewed patients newly diagnosed with Peyronie's disease and treated with tamoxifen from January 2008 to November 2010. Only patients with tamoxifen used as the first treatment for Peyronie's disease diagnosed for the first time were included. Patients with use of combination regimens or concomitant PDE5 inhibitor use were excluded.

In all patients, a medical history was obtained including states of concomitant disease of hypertension and diabetes, as well as a history of pelvic trauma. Penile ultrasonography and 20 μg prostaglandin E1 induced pharmacologic erections were performed for measurement of longest plaque length and presence of calcification was identified on penile X-ray. The degree of curvature following injection was also noted. As erectile dysfunction is a primary feature of Peyronie's disease, serum testosterone levels were also evaluated during the initial management of these patients.

The patients were grouped into those in an acute phase and those in a chronic phase based on the presence of painful erections at the beginning of tamoxifen treatment. Progression of Peyronie's disease was defined as either an enlargement or calcification of plaque on follow up, or the appearance of plaque if no definite plaque was previously identified. Plaque size on follow up was estimated by the longest diameter of ultrasonographic hyperechoic lesion on a manually stretched length. To account for variability in measurement, enlargement was only defined when plaque length increase was greater than 20%. Time to progression was defined as the median point in time between the outpatient visit in which progression was identified and the previous visit in which progression had not been determined.

Results

1. Initial patient characteristics

Overall a total of 104 patients received tamoxifen as the first line treatment for Peyronie's disease during the study period. The average patient age was 56.9±9.6 years (range: 34～75 years). Hypertensive patients constituted 19.2% of the patients, while 24.0% of the patients were diabetic. Patient history revealed that 21.2% of the patients had a definite history of pelvic or genital trauma.

On presentation, the average size of the plaque was 1.6±1.1 cm. However, on ultrasonography, 42.3% of the patients showed no significant alteration in echogenicity, and only 14.4% of the patients showed calcification on X-ray. The average degree of curvature was 18.3±3.9°. The location of the plaque was predominantly in the middle third by length (65.4%), while 27.9% were located more proximally and 5.8% more distally. Only one case showed clear multicentric plaques.

While all patients visited the outpatient clinic with complaints of some degree of curvature, 48.1% (n=50) of the patients had reported pain on erection. These patients were considered to be in the acute phase of Peyronie's disease. The mean average duration of treatment was 15.8±12.1 months (range: 3～48 months).

The comparisons of the two groups' initial characteristics are listed in Table 1. There was no significant difference between the two groups concerning initial plaque size, degree of curvature, level of serum testosterone, presence of hypertension or diabetes, or previous history of trauma. However, patients in the acute phase were significantly younger than patients in the chronic phase (54.9±9.8 vs. 59.2±8.9 years, p=0.02).

2. Treatment outcomes

At the termination of treatment, 72.1% (n=75) of all the patients showed progression. Newly formed calcifications had appeared in 14.4% (n=15) of the patients, with no significant difference between the acute and chronic patients (18.0% vs. 11.1%, respectively. p=0.24). Plaque enlargement was found in 57.7% (n=60) of the

Table 1. Initial characteristics of the patients on presentation, with univariate and multivariate analysis of factors associated with patient disease state

	Overall	Acute	Chronic	Univariate	Multivariate
n	104	50	54		
Treatment (months)	15.9±13.8	14.2±13.2	16.8±15.7	0.47	0.31
Age (years)	56.9±9.6	54.9±9.8	59.2±8.9	0.02	0.19
Hypertension	19.2% (n=20)	18.0% (n=9)	20.4% (n=11)	0.48	0.10
Diabetes	24.0% (n=25)	26.0% (n=13)	22.2% (n=12)	0.41	0.58
Trauma	21.2% (n=22)	22.0% (n=11)	20.4% (n=11)	0.51	0.79
Testosterone (ng/ml)	5.2±2.2	5.0±2.5	5.5±1.7	0.45	0.57
Curvature (°)	18.3±3.9	20.0±4.5	16.7±2.6	0.15	0.24
Size (cm)	0.9±1.2	0.9±1.3	1.0±1.1	0.83	0.81

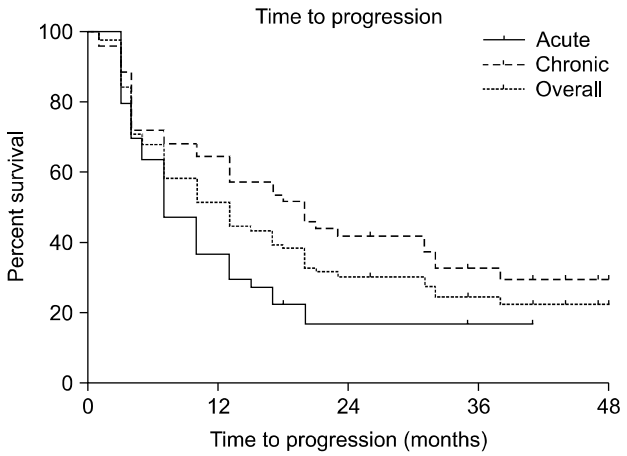

Fig. 1. Progression of Peyronie's disease in patient receiving tamoxifen.

patients with the acute patients showing a higher proportion with enlargement (66.7%, n=36) than the chronic patients (48.0%, n=24) (p=0.04).

Overall, 78.0% (n=39/50) of patients were initially treated at the acute phase and 66.7% (n=36/54) of patients showed progression on follow up (p=0.14). Time to progression was plotted between the two groups showing a median survival to progression as 7.0 months and 20.0 months for acute and chronic patients, respectively. A Mantel-Cox test of survival curves showed significant delay of progression in chronic patients (p=0.01), with a hazard ratio of 0.49 (95% CI: 0.30～0.82) for a patient to progress as compared to patients in the acute phase (Fig. 1). Pain relief was found in 80.0% (n=40) of patients in the acute phase. There were no significant differences in any initial parameters of pain relief and pain persistence among the acute patients.

On multivariate analysis predicting treatment outcomes based on patient comorbidity status and trauma history, plaque size, penile curvature, presence of pain and hypogonadism (defined as serum testosterone below 3.5 ng/ml), and age group (divided at 55 years) showed no single factor was predictive of treatment outcome.

Discussion

The natural history of Peyronie's disease is obscure. Generally, it is characterized as an inflammatory acute phase followed by a stable chronic phase; however, these definitions are not clearly established. Most previous studies have defined the acute phase as lasting 12 months.[2,9] Hellstrom[7] identified the acute phase within an initial 12 to 18 months characterized by painful erections and worsening deformity. However, as some studies have noted, up to 15% of patients have been unaware of the onset of their disease, making a definition based on onset time difficult to implement.[10] Other studies have presented classification of progression based on initial findings and eschewed chronologic classification. Bekos et al[11] suggested classification based on ultrasonographic findings, where early hyperechogenecity without an acoustic shadow suggested the acute phase of Peyronie's disease, and appearance of obvious calcification characterized the chronic phase. As the focus of this study was to observe progression of patient symptoms within varying follow-up time frames, we also could not incorporate

a fixed chronologic definition for progression, and elected to identify the acute phase based on the most significant symptom representative of the acute phase, i.e., pain on erection. As previous studies have shown that only 21.8～52.6% of patients present with pain as their initial symptoms, the current study may have underestimated the proportion of patients that were in the acute phase as compared to studies that have elected a chronological definition.[9,10] As such, the median time to progression was shorter than the generally defined duration of the acute phase in other studies.

While the true pathogenesis of Peyronie's disease remains unknown, fibrosis of the tunica albuginea is considered a major contributor to morbidity in patients with Peyronie's disease. Ralph et al[12] reported that the cytokine TGF-β, which is released by platelets and activated macrophages, appears to play a central role in the inflammatory response and in wound healing. Earlier reports have suggested positive results, such as a decrease in plaque size, relief of pain, and improvement of penile morphology; however these studies were mostly short-term studies.[6,13] The present study, though retrospective, shows long-term follow up results of a mean 15.9±13.8 months (range 3～48 months). As outcome measures are different in our study, direct comparison is unavailable. However, inhibition of progression at 3 months was 80.0% and 88.9%, respectively, for acute and chronic patients. Unfortunately these rates continually decline as treatment progresses, reaching only 16.8% for acute patients and 29.7% for chronic patients by 48 months.

Pain relief as an independent outcome for acute patients showed an excellent 80% relief rate. This is similar to previous reports, which showed 66.6% pain relief with treatment by placebo, in contrast to much lower rates of improvement for physical characteristics, such as penile deformity (46.1%) and plaque size (31.7%).[6] Unfortunately, while our result lacks any contrast for comparison, previous studies also show no significant benefit over placebo (75.0%). Thus, pain relief or delayed progression of the disease during the chronic phase cannot be conclusively attributed to the treatment effect of tamoxifen.

Peyronie's disease is a frequently progressive disorder. While earlier reports suggested a 50% spontaneous resolution rate, recent studies are more skeptical.[2,14] One study followed 246 men newly diagnosed with Peyronie's disease for 1 year without treatment, after which 12% improved, 40% remained stable, and 48% worsened.[2] Our study also showed 55.5% of all participants had worsened at 1 year, despite treatment with tamoxifen. Our study is limited by the lack of a placebo for signifying the natural progression in both the acute and chronic phases of Peyronie's disease. Nevertheless, the current study clear shows progression of Peyronie's disease in the acute phase and continuing on in the chronic phase.

The etiology of Peyronie's disease remains unclear. Separately, hypertension, diabetes, and a clear history of trauma each represent only about 20% of the etiology in our study. Combined, only 48.6% (n=51) of the cases were explainable by these factors. Old age was not as significant a cause of disease progression when viewed as a combined effect with other factors. In fact, 8.6% (n=9) were 40 years old or younger in concordance with previous reports citing approximately 10% of Peyronie's disease cases as being under 40 years of age (Fig. 2).[9,15]

Overall this study confirms the lack of treatment benefit of tamoxifen. Furthermore, continued progression by plaque size increase, plaque formation, and calcification seems to continue, despite a blunted rate in the chronic phase as well as the acute phase. Currently, other medical treatments such as potassium

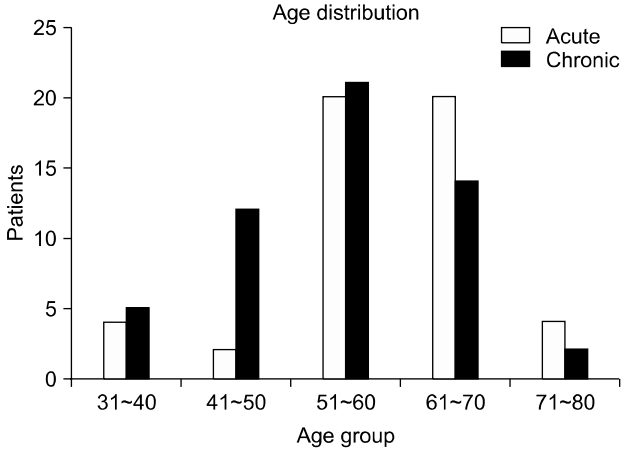

Fig. 2. Age distribution of Peyronie's disease.

para-aminobenzoate or acetyl-L-carnitine may show comparable benefits over tamoxifen; however, our study shows that short-term improvement must be interpreted with caution. Topical or injection therapies have also reported variable results with no definite preference for the acute or chronic phase of the disease. Meanwhile, shock wave and surgical treatments have mostly been recommended for chronic cases.[4]

Finally, in conducting this study and comparing the results to previous studies, a clear and definite outcome measurement that can be used for either acute or chronic Peyronie's disease is lacking. Subjective symptoms such as pain relief have shown to diverge from objective measurements, and objective measurements are heavily reliant on proper pharmacologic induction of erection during measurement, which may also be dependent on the severity of Peyronie's disease progression.

Conclusions

Peyronie's disease is a progressive disease both during the acute and chronic phase. In accordance with previous, the long term outcome of tamoxifen showed no significant treatment benefit.

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