Doxazosin, a Selective Alpha-1 Blocker, in the Treatment of Premature Ejaculation

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ABSTRACT

Objective: Pharmacotherapy for premature ejaculation has been widely used for years. The efficacy of antidepressants, especially SSRIs, has been confirmed by many randomized controlled studies. The orthosympathetic activity on the ejaculatory system is a well-studied entity. In this study, our purpose is to evaluate the efficacy of a selective α-1 blocker, doxazosin, in the treatment of premature ejaculation.

Material and Methods: The study comprised 42 patients (mean age 39.11) out of a total of 44 patients with PE who were referred to Ege University Urology Outpatient Clinic from September 2000 to June 01. Among them, 27 patients were asked to use a daily dose of 4 mg of the α-blocker doxazosin for 6 weeks. The control group consisted of 15 patients who were asked to use 4 mg of placebo (starch) in the same way as doxazosin. After a therapy of 6 weeks, all the patients were interviewed to assess the efficacy of the therapy and to report any side effects.

Results: There was a significant increase in the latency of ejaculation with doxazosin in 12 out of a total of 27 patients (44.40%) compared to placebo, where only 2 out of 13 patients (13.30%) showed a similar effect. The effect of doxazosin was found to be statistically significant (p<0.043). The side effect profile showed no significant difference between doxazosin and placebo.

Conclusion: The result of our study indicates that doxazosin is safe and effective in patients with PE. Its activity is comparable to phenoxybenzamine and clomipramine, as reported in the literature. Additionally, its significantly lower and milder adverse effect profile appears to be an advantage.

Keywords: Premature ejaculation; Treatment; Selective alpha-1 blocker; Doxazosin; Urology patients

INTRODUCTION

Premature ejaculation is one of the most frequently seen disorders among male sexual dysfunctions. Despite being defined in various ways, there is no absolute definition. Currently, there are no epidemiologic standards for evaluating the effect of factors such as age, sexual experiences, and libido on sexual intercourse (1). In various studies, the incidence of premature ejaculation was found to be between 30% to 40% among adult men (2). The primary challenge lies in selecting the criteria to describe prematurity (3). As a result, there are various descriptions of PE, such as ejaculation before 15 intravaginal movements of the penis, absence of female orgasm during intercourse, ejaculation before penetration or at the beginning of intercourse, and premature ejaculation occurring in at least 50% of intercourse occasions. In addition to these subjective criteria, a number of objective descriptions are determined through neurophysiologic measurements. These include ejaculation before 2 minutes of intercourse, SEP (Somatosensory Evoked Potentials) stimulation threshold less than 40v or 6-9 amper, SEP reflex transmission time less than 42m/s, dorsal nerve-SEP transmission time less than 40 m/s, dorsal nerve SEP amplitude greater than 2 mv, and ejaculation time by vibration and visual stimulation less than 3 minutes.

Ejaculation is a result of alpha receptor activation that integrates with central pathways and peripheral reflex stimulations (4). Numerous methods and medications have been used for premature ejaculation. Some of the traditional methods include trying to have multiple orgasms during sexual intercourse, masturbating before penetration, using condoms, and applying local anesthetic ointments on the glans penis.
In addition to these traditional methods, sedatives, antidepressants, and phenothiazines are widely used in the treatment of PE. However, their exact effect on ejaculatory latency is not definitively known, and it remains controversial whether PE is solely an organic disorder.

Neurophysiological studies have shown that the ejaculatory reflex time threshold value is lower in patients with PE compared to normal men. Sacral and cortical evoked potential studies have also indicated that in patients with PE, the activity of the motor neurons of the pudendal nucleus may be altered by the central nervous system or there may be a hyperstimulative reflex status (5-9).

Various therapeutic agents are used in the treatment of PE, which can be classified into three major groups: agents that affect the central nervous system (such as SSRIs, lorazepam, clomipramine, etc.), agents that affect the sympathetic nervous system (such as phenoxybenzamine, propranolol), and agents that inhibit the tumescence state caused by ejaculation (such as intracavernosal injections).

In this placebo-controlled, single-blind study, our purpose is to evaluate the efficacy of a selective alpha-blocker, doxazosin, in patients with PE.

**MATERIAL and METHODS**

The study comprised 42 patients (mean age 39.11) out of a total of 44 patients with PE who were referred to Ege University Urology Outpatient Clinic from September 2000 to June 2001. One patient with a psychiatric disease and another with erectile dysfunction with PE were excluded from the study.

PE was defined as involuntary ejaculation within 2 minutes of penetration on at least 50% of intercourse occasions during the previous 6 months. The inclusion criteria were a regular relationship with a partner for at least one year and a history of premature ejaculation for at least 6 months. All of the patients were asked to complete the questionnaires before participating in the study.

The exclusion criteria were as follows:

- Erectile dysfunction with or without loss of libido
- Men with chronic diseases (uncontrolled hypertension, diabetes mellitus, history of myocardial infarction, orthostatic hypotension)
- Use of alpha-blocker treatment in the previous two months
- The use of agents that affect sexual function
- Concurrent urinary infection

Complete urinary analysis and prostatic fluid analysis were performed, and two patients with an infection were included after receiving medical treatment. All the patients were informed about the study, and their approval was obtained.

Twenty-seven patients were asked to use a daily dose of 4 mg of the alpha-blocker doxazosin for 6 weeks. The control group, consisting of 15 patients, were asked to use 4 mg of placebo (starch) in the same way as doxazosin. After the 6-week therapy period, all the patients were interviewed to evaluate the efficacy of the therapy and any potential side effects. Efficacy was assessed based on ejaculatory latency time, as well as partner and patient satisfaction. The patients were asked to measure the ejaculation latency time using a stopwatch.

Statistical analysis was performed using SPSS 22.0 (SPSS, Inc., Chicago, IL, USA). Mean and descriptive analysis measures were used for the characteristics of the patients. Chi-Square statistics were employed for categorical data, comparing the categorical variables (n) with percentages. An unpaired Mann-Whitney U test was used for continuous variables. Statistical significance was considered if p<0.05.

**RESULTS**

The mean age of the patients was 39.11 years. Among the patients, 7 were in the 20-30 age group (16.6%), 14 were in the 30-40 age group (33.3%), 13 were in the 40-50 age group (30.9%), and 8 were above the age of 50 (19.04%).

In 30 patients, premature was present for more than 2 years, in 9 patients it was present for 1-2 years (21.42%), and in 3 patients, it was present for less than a year.

The latency time of ejaculation was less than 1 minute in 32 patients (76.19%) and within 1 to 2 minutes in the remaining 10 patients (19.04%).

The patients’ partners’ approach to this problem was also questioned in this study, and 36 patients found their partners supportive.

There was a significant increase in the latency of ejaculation with doxazosin in 12 out of a total of 27 patients (44.40%), compared to only 2 out of 13 patients (13.30%) in the placebo group. The effect of doxazosin on increasing ejaculation latency was statistically significant (p<0.043).

The side effect profile of doxazosin did not show a significant difference compared to placebo. Only one patient had to discontinue the medication due to hypotension. Additionally, 7 patients showed minor improvement in ejaculation latency, but it remained below 2 minutes. These 7 patients, along with the patient who discontinued due to hypotension, are considered to be in the group with no significant improvement.
The peripheral mechanisms in PE underscores the role of peripheral factors. Patients with PE receive strong cortical sensory stimulation from their genitalia, leading to heightened penile blood flow. Other factors such as neurophysiological and reflex mechanisms are also being recognized as contributing to the pathophysiology of PE. Today, PE is not solely considered a psychogenic disease, although anxiety appears to be a variable in this condition. Other factors such as neurophysiological and reflex mechanisms are also being recognized as contributing to the etiology of PE. This broader understanding of PE’s pathophysiology has led to the exploration of various treatment options beyond just psychological interventions. As a result, pharmacological agents targeting different aspects of the ejaculatory process have been investigated and found to be effective in the management of PE. Further research is needed to fully elucidate the multifaceted nature of PE and develop more tailored and effective treatment approaches.

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**DISCUSSION**

Ejaculation and emission are basically under the control of the sympathetic nervous system. The sympatholytic agents can cause ejaculatory insufficiency as they inhibit the contractions of the seminal vesicles, ampulla and ductus deferens (10). Some neurophysiologic and vascular differences are determined between the patients with primitive psychogenic PE and normal men. In PE there is a decrease in bulbocavernous reflex latency and high amplitudes of evoked sacral potentials in perianal measures. These events can be explained by orthosympathetic nervous system hyperactivity. Recently, the theories about the pathophysiology of PE have encountered some differences. Today, PE is not solely considered a psychogenic disease, although anxiety appears to be a variable in this condition. Other factors such as neurophysiological and reflex mechanisms are also being recognized as contributing to the etiology of PE. This broader understanding of PE’s pathophysiology has led to the exploration of various treatment options beyond just psychological interventions. As a result, pharmacological agents targeting different aspects of the ejaculatory process have been investigated and found to be effective in the management of PE. Further research is needed to fully elucidate the multifaceted nature of PE and develop more tailored and effective treatment approaches.

Table 1: Results of Alpha-1 Blocker and placebo treatment given to patients

<table>
<thead>
<tr>
<th>No of patients</th>
<th>Alpha-1 Blocker treatment group</th>
<th>Placebo group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>27</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Significant improvement</td>
<td>12</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>No or insufficient improvement</td>
<td>15</td>
<td>13</td>
<td>0.043</td>
</tr>
<tr>
<td>%</td>
<td>44.40</td>
<td>13.10</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2:** Comparison of patients receiving Alpha-1 Blocker and placebo treatment

Alpha receptor blockers are thought to exert their effect by counteracting this somatic hyperstimulative status, thus delaying the latency of orgasm in these patients. Additionally, these blockers diminish the tonus of muscle cells in seminiferous tubules, contributing to their therapeutic effect on the ejaculatory system. The complex interplay between cortical and peripheral mechanisms in PE underscores the need for a comprehensive approach in its treatment and highlights the potential of alpha receptor blockers as a promising therapeutic option.

After the efficacy of sympatholytic agents in PE was demonstrated, many of them were subsequently tested in this area. Their effect on PE depends on the suppression of genitalia contractions during emission.

Jt Hsieh et al., in an experimental study, demonstrated the suppressive effect of sympatholytic agents on the contractive response to ENS in the seminal vesicles of rats (11). Alfazosin, terazosin, phenoxybenzamine, yohimbine, WB-4101, and RX821102 were all compared in a study for their efficacy and side effects. Although high doses of phenoxybenzamine showed efficacy in PE treatment, its long-term use is limited due to possible carcinogenic potential and basic side effects like dry ejaculation. After the efficacy of doxazosin, alfuzosin, and terazosin on PE was shown, alpha-1 adrenergic components were found to be responsible for the inhibitory effect of phenoxybenzamine on rat seminal vesicles. In a preliminary study with high doses of prazosine, a maximal inhibitory effect of up to 68% was reached, although its relative effect was not as pronounced as phenoxybenzamine or WB-4101.

The findings of this study have shown the significant effect of a-1 adrenergic stimulation on rat's seminal vesicle contractions. RX821102, a selective a-2 blocker, was found to be ineffective in inhibiting the rat's seminal vesicle contractions to electric nerve stimulation, indicating that the a-2 adrenergic effect plays no role in seminal vesicle contraction. On the other hand, yohimbine, another a-2 receptor blocker that also affects the a-1 receptors at high concentrations, was able to inhibit seminal vesicle contractions in rats. This efficacy is possibly due to its peripheral alpha-1 adrenergic blockade effect, which becomes prominent at higher concentrations. Moreover, yohimbine was found to have fewer side effects compared to phenoxybenzamine.

As a result of these studies, the efficacy of sympatholytic agents in PE seems to be related to their alpha-1 receptor blockade activity. However, it is also evident that although phenoxybenzamine and yohimbine appear to be the most effective sympatholytic agents, their side effect profiles may limit their widespread use.

In a prospective study, Belletta et al. demonstrated subjective improvement in latency time from penetration to ejaculation in 8 out of 15 patients treated with phenoxybenzamine (12). Our study results were consistent with those of Cavellini et al. (4), who found improvement in ejaculation latency with alphazosin and terazosin in a placebo-controlled study involving patients with premature ejaculation resistant to psychotherapy.
Specifically, they reported improvement in ejaculation latency in 42 out of 91 patients treated with alphazosin, 48 out of 91 patients treated with terazosin, and 21 out of 91 patients treated with placebo.

Ertekin et al. conducted a study where they found that in normal individuals, the sudomotor sympathetic activity is diminished and suppressed in the genitalia during sexual stimulation, while there is no change in sudomotor sympathetic activity in the hand (9). However, in patients with premature ejaculation (PE) who achieved an erection with papaverine and sexual stimulation, they observed an increased sympathetic activity in the genitalia, which was unexpected to diminish, and no difference in regional sudomotor sympathetic activity. Based on these findings, they concluded that such variable sympathetic activity in the corporal system may play a role in the pathogenesis of PE (9).

**Limitations:** The limitations of this study can be listed as the fact that the study was conducted in only one province, hospital and polyclinic.

**CONCLUSION**

Our study demonstrates that doxazosin is a safe and effective treatment option for patients with premature ejaculation (PE). Its efficacy is comparable to that of phenoxybenzamine and clomipramine, as reported in the literature. Moreover, the remarkably lower incidence of minor side effects associated with doxazosin makes it a favorable choice.

The mean age of the patients included in our study was 39.11 years, which raises interesting considerations regarding sexual experience and its impact on penetration and intercourse abilities (13). However, further epidemiological trials are needed to draw more reliable conclusions across various age groups.

Furthermore, the findings of our study contribute to the growing understanding of the pathophysiology of PE, particularly in relation to sympathetic activity in the genitalia during sexual stimulation (9). As research continues to shed light on the underlying mechanisms of PE, the development of effective treatment approaches like doxazosin becomes increasingly important in improving the quality of life for patients suffering from this condition.

Overall, our study supports the use of doxazosin as a valuable therapeutic option for PE and highlights the need for further investigations to enhance our understanding of this complex sexual disorder.

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**Ethical approval:** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions.

**REFERENCES**