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Original Article

A Randomized Double-blind Placebo-controlled Trial to Assess the Effect of Tamarind seed in Premature Ejaculation

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Abstract

Background: This randomized clinical trial was aimed to evaluate the effect of oral use of tamarind seed powder as an herbal product in patients affected by premature ejaculation (PE). **Materials and Methods:** In this study, 75 patients randomized in tamarind group (25 patients received daily 130 mg tamarind seed powder), paroxetine group (25 patients received daily 20 mg paroxetine), and placebo group (25 patients). Patients received the treatment regimen for 4 weeks. The primary outcome was intravaginal ejaculatory latency time (IELT). The secondary outcomes were PE diagnostic tool score, sexual function using International Index of Erectile Function (IIEF), and complications. Studied sexual functions include erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. **Results:** The mean of IELT in tamarind, paroxetine, and placebo groups at baseline was 35.2 ± 26.5, 38 ± 27.6, and 44 ± 34.9 s and at the end of study was 49.5 ± 48.2, 147.4 ± 209.6, and 46.9 ± 37.6 s, respectively, which in paroxetine group significantly increased compared to other groups. IIEF scores for orgasmic function and intercourse satisfaction for paroxetine after treatment significantly increased than that of other groups. The differences between tamarind and placebo groups for studied variables were not statistically significant. The mean of increases in IELT for tamarind, paroxetine, and placebo groups was 14.35 ± 34.3, 109.4 ± 213.4, and 2.9 ± 9.3 s, respectively, which in paroxetine group was significantly higher than other groups and in tamarind group was significantly higher than placebo. **Conclusions:** Paroxetine was significantly better than tamarind seed powder and placebo although side effect in paroxetine was more frequent. IELT significantly more increased in tamarind group compared to placebo.

Keywords: *Complementary medicine, paroxetine, premature ejaculation, tamarind seed, Tamarindus indica*

Introduction

Sexual dysfunction is a common condition affecting both men and women and preventing them from experiencing satisfaction from the sexual activity. Erectile dysfunction and premature ejaculation (PE) are the main and prevalent sexual complaints among men.[1,2] PE as the most prevalent sexual problem in men is defined as persistent ejaculation with minimal sexual stimulation before or soon after penetration, on which the individual has minimal voluntary control over.[3] The history of PE is probably as old as human history, and was mentioned in medieval Persia as well as other antiquity and the medieval period.[4] Epidemiologic studies estimated the prevalence of PE ranging from 10% up to 40%.[5-7] Low self-esteem, interpersonal difficulty, and mental health problems can be caused by PE that can affect both the male and female partner.[8,9]

The etiology of PE has not still been fully defined, but it is believed that this condition is multifactorial, and associations with psychological, environmental, endocrine, and neurobiological factors have been made. Therefore, treatments of PE may include both behavioral and/or pharmacological interventions.[1-11]

A number of drugs with varying degrees of success have been used treating PE. Antidepressants, local anesthetic agents, and phosphodiesterase type 5 inhibitors are currently used by clinicians for the management of PE.[12] At present, fluoxetine, sertraline, paroxetine, and citalopram are common selective serotonin reuptake inhibitors used in the treatment of PE.[13] Dapoxetine is the only approved oral drug to treat PE but it is expensive and is not available in many countries.[14] The ideal treatment for PE would be a novel

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medication with rapid-acting properties which is effective without sexual or systemic side effects.

In the recent years, in many countries, the use of various methods of alternative medicine has increased. Various herbal products in traditional and alternative medicine have been prepared for men and women seeking improvement in their sexual life.[15] In some previous studies,[16-21] a variety of herbal products were assessed in patients suffering from PE, and different and limited findings reported for these surveys and the efficacy of most herbal agents in treating sexual problems remain uncertain.

Tamarindus indica is a medicinal plant with high antioxidant activities. Different parts of the plant are used in food products, industries, and medicine.[22] Some previous studies reported the effects of tamarind seed in medical practice for some purposes.[23-27] In Iranian traditional medicine, tamarind seed powder was recommended for the management of PE, but there is no evidence-based information for its efficacy. In the present study, we assess the possible therapeutic role of tamarind seed powder in patients affected by PE through a randomized controlled trial.

Materials and Methods

This randomized, double-blind controlled trial was conducted between March and December 2015, on 75 male patients with PE who referred to urology clinics in Shiraz, Iran. The Ethics Committee of Shiraz University of Medical Sciences approved this study; also, this study is registered at the Iranian Registry of Clinical Trials [IRCT2015051422281N1]. All patients were informed about the procedure of the survey and written informed consent was obtained from all of them. PE was diagnosed by allocating the International Society for Sexual Medicine guideline.[28] Patients were eligible if their ejaculation, always or nearly always, occurs prior to or within about 2 min of vaginal penetration. Other inclusion criteria were age between 20 and 50 years, being married and in a stable sexual relationship with a female partner for at least 6 months, having sexual intercourse once a week or more often and the Premature Ejaculation Diagnostic Tool (PEDT) score >8.[29] The exclusion criteria were a history of psychiatric disorders requiring therapy/medication, diabetes mellitus, renal insufficiency, liver diseases, dyslipidemia, hypertension, hypothyroidism or hyperthyroidism, cardiac arrhythmias, other sexual dysfunctions, and sexual dysfunction in the partner. In addition, men who have been taking medications that could have affected their ejaculatory function were excluded.

Eligible patients were randomly divided into three 25-member groups, using random-maker software "Random Allocation" (Isfahan, Iran). Patients in tamarind group received 130 mg of tamarind seed powder and 260 mg of sugar one time per day. Patients in paroxetine group received one time per day of 20 mg of paroxetine. Control group included 25 patients who received one time per day placebo. To prepare the tamarind seed powder, first, the seeds were separated from the shell and then changed it into powder. The whole seed powder should pass 80-mesh screens. Hence, the seed powder was mixed with 2-fold of sugar, and for each capsule of tamarind, 380 mg of mixture was used. Dose of tamarind seed powder in this study was the lowest recommended dose in Iranian traditional medicine. All treatments were taken for 4 weeks and patients were instructed to have twice weekly vaginal sexual intercourse during treatments and were not permitted to use condoms or topical anesthetics. To maintain blinding, patients and nurses were unaware of the treatment allocation and all drugs used in the study were prepared in the same capsules and were formally manufactured as the same in Faculty of Pharmacy, Shiraz University. Drugs were set in a coded envelops and eligible patients received the content of one of these envelops by random.

Collected data included age, education level, intravaginal ejaculatory latency time (IELT), PE status, sexual function, and complications. IELT was measured to assess the effectiveness of the treatment and was defined as the time between the start of vaginal intromission and the start of intravaginal ejaculation. Patients were asked to measure IELT in any sexual intercourse during 2 weeks before starting medications and the average of these times was set as baseline IELT. PE status was evaluated by PEDT including five questions with a total of 20 score. A PEDT score of 0–8 was considered as not having PE, score of 8–10 as suspect to PE, and scores of 11 and above as having PE. Sexual function was measured with the International Index of Erectile Function (IIEF). IIEF is a brief, self-administered scale that consists of 15 questions assessing five domains of male sexual function:[30,31] six items to evaluate erectile function (questions 1–5 and 15), two items to evaluate orgasmic function (questions 9 and 10), two items to evaluate sexual desire (questions 11 and 12), three items to evaluate intercourse satisfaction (questions 6–8), and two items to evaluate overall satisfaction (questions 13 and 14). Higher score of IIEF indicates better sexual functioning. All variables were recorded before and at the end of 4-week treatment period.

The comparison of mean formula for the level of IELT was used to calculate the sample size with $\alpha = 0.05$ and 80% power, based on values in Falahatkar *et al's*.[32] study. All statistical analyses were done using SPSS software for Windows (SPSS, Inc., Chicago, IL, USA, version 20). Descriptive data are reported as mean ± standard deviation, median (IQR), or number (percentage). Repeated measurements of ANOVA, ANCOVA, and Chi-square test were used to compare all the studied variables between groups. The mean of differences among the three study groups after treatments compared to baseline for the studied

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variables was analyzed using one-way ANOVA with Bonferroni test as *post hoc* tests. The level of significance is considered to be <0.05.

Results

Of 94 reviewed patients, 19 patients did not enter to the study (15 patients were not eligible and four patients refused informed consent). Seventy-five patients were eligible and randomly assigned into three intervention groups. Patients were followed up for 4 weeks and during follow-up three patients did not desire to continue and excluded. Finally, 72 patients with a mean age of 36.7 ± 6.6 years (in placebo, paroxetine, and tamarind, 24, 23, and 25 patients, respectively) completed the study and their data were analyzed [Figure 1]; the mean of age was not significantly different between the three groups.

Table 1 illustrates the mean scores on IELT, PEDT, and IIEF for the three study groups. Results from repeated measurements of ANOVA with Bonferroni test as *post hoc* analyses showed that the mean of IELT, IIEF orgasmic function, and IIEF intercourse satisfaction scores in paroxetine group after treatment significantly increased than that of the other groups. The mean of IIEF sexual desire and IIEF total scores in paroxetine group after treatment significantly increased compared to placebo group. The mean of PEDT, IIEF overall satisfaction, and IIEF erectile function scores was not significantly different among the study groups. Between tamarind and placebo groups, there was no significant difference for all studied variables. Furthermore, as shown in this table, after ANOVA analysis and controlling the effect of baseline values as covariates, after treatment, only IIEF sexual desire score was not significantly different among the three groups but all other studied variables were significantly different among the study groups.

Table 2 shows the comparison of differences among groups after treatments compared to baseline for IELT, PEDT, and IIEF scores. As shown in this table, the mean of increases in paroxetine group was significantly more than that of other groups. In addition, the mean of changes in PEDT, IIEF overall satisfaction, IIEF intercourse satisfaction, and IIEF total scores among the three groups after treatment was statistically significant. The mean of changes in IIEF orgasmic function, IIEF orgasmic function, and IIEF sexual desire scores was not statistically significant. *Post hoc* analyses showed that the mean of changes between paroxetine with tamarind group and paroxetine with placebo group was statistically significant and between tamarind group and placebo group the mean of changes was not statistically significant.

Comparison of adverse events occurring among study groups is shown in Table 3. As shown in this table, 43% of patients in paroxetine group reported adverse event whereas one patient in tamarind group and one patient in placebo group reported adverse event (P = 0.0002). The most common adverse events were drowsiness and nausea which were prevalent in paroxetine group than that of other groups. The frequency of constipation and reduced libido was not significantly different among the three groups.

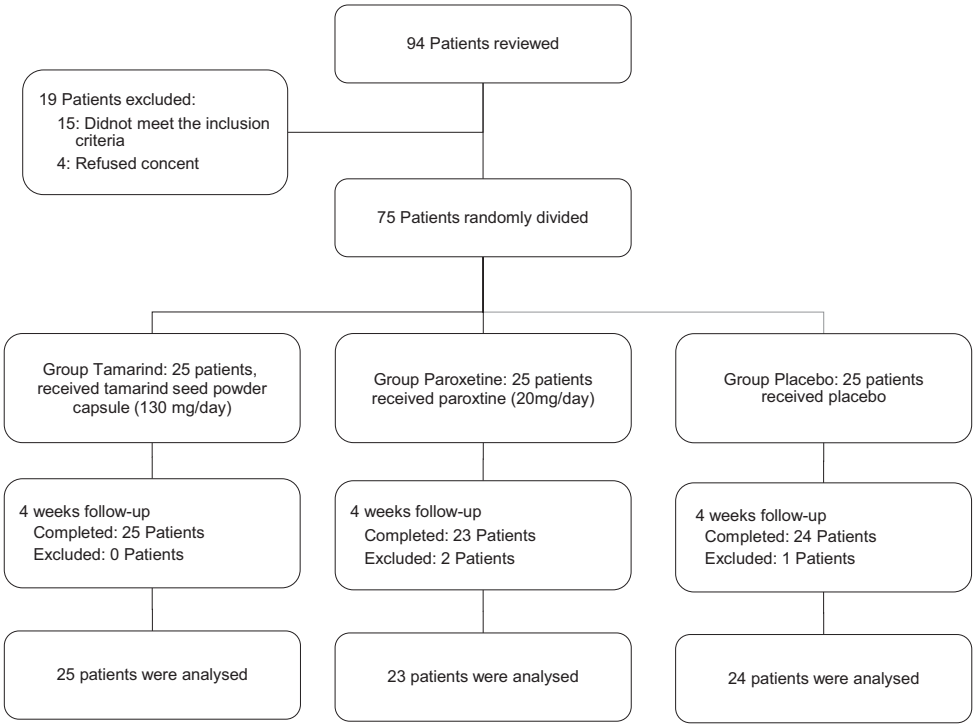

Figure 1: Flowchart depicts patients entered to the study who were divided into the study groups and analyzed

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Table 1: Intravaginal ejaculation latency time, premature ejaculation diagnostic tool, and International Index of Erectile Function Scores before and after study between groups

Variables	Group			*P**	*P*†
	Tamarind (*n*=25)	Paroxetine (*n*=23)	Placebo (*n*=24)		
IELT					
Before	35.2±26.5	38±27.6	44±34.9	0.015††	0.007
After	49.5±48.2	147.4±209.6	46.9±37.6		
PEDT score					
Before	14.8±3.2	15.6±2.8	15.4±2.7	0.25	0.003
After	13.7±3.2	12±4.7	15±2.7		
IIEF erectile function score					
Before	21.2±5.5	21.3±5.4	19.4±6.4	0.26	0.044
After	22.4±4.6	23.2±4.5	20.3±5.7		
IIEF orgasmic function score					
Before	6.5±2.1	7.9±1.4	6.7±2.1	0.001††	<0.0001
After	6.8±1.3	8.4±1.1	6.5±1.3		
IIEF sexual desire score					
Before	6.9±1.9	7.6±2	6.3±1.4	0.015**	0.11
After	7.2±1.6	7.9±1.2	6.6±1.3		
IIEF intercourse satisfaction score					
Before	7.6±2.4	8.6±2.1	7.1±2.6	<0.0001††	<0.0001
After	7.9±2.1	10.4±2.5	6.9±2		
IIEF overall satisfaction score					
Before	5.5±2.3	5.1±2.2	5.7±2.2	0.48	<0.0001
After	5.8±1.9	7.2±2.5	5.2±2		
IIEF total score					
Before	47.7±11.8	49.5±10.2	44.8±12.3	0.024**	<0.0001
After	50.1±9.2	57.2±9.2	45.6±10.3		

Data expressed as mean±SD. *P* values calculated by *Repeated measurements of ANOVA, †ANCOVA (baseline values were controlled as cofounder). *Post hoc* tests (Bonferroni) show significant differences between, ††paroxetine with tamarind and placebo and between **tamarind with placebo. IELT: Intravaginal ejaculation latency time, PEDT: Premature ejaculation diagnostic tool, IIEF: International Index of Erectile Function

Discussion

PE is a common condition affecting personal distress which may in turn affect the relationship of the man with his partner. Nearly, one out of five men in the world suffers from PE.[14] For many decades, the quest for an effective tablet to the treatment of PE has been increased. However, limited understood about the pathophysiology of PE, the clinician has faced a real challenge to treat PE. A number of drugs with varying degrees of success have shown in treating PE. But, at the present time, dapoxetine is the only licensed drug in the treatment of PE only in some countries. Dapoxetine is not available in many countries and also the cost of the drug is high, so there is a search of new option in the medical management of PE, especially in developing and middle-income countries. In the recent years, in many countries, the use of various methods of alternative medicine has increased. Various surveys on traditional and alternative medicine have highlighted the widespread use of herbal products. And, around the world, these have become an important and indispensable part of public health care. In this randomized study, we evaluated the effect of tamarind seed powder on PE compared to paroxetine and placebo. Findings revealed that no significant difference was detected in the end points between tamarind seed powder and placebo. Paroxetine was significantly better than tamarind seed powder to improve IELT in PE patients but side effect in paroxetine group was significantly more frequent than that of tamarind group. The dose of tamarind seed powder used in our study is the lowest recommended dose in traditional medicine texts and it can be used in higher dose. So, higher dose can be assessing in further clinical trials.

To the best of our knowledge, the present study is the first to assess the effect of tamarind seed powder on PE. Of note, after 4 weeks' use of tamarind, although there was no difference between tamarind and placebo groups, the average of increase in IELT in tamarind group was more than placebo group (14.9 vs. 2.9, respectively) and all

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Table 2: Mean differences of studied variables after intervention compared to baseline

Characteristics	Group			*P*
	Tamarind (*n*=25)	Paroxetine (*n*=23)	Placebo (*n*=24)	
IELT	14.35±34.3	109.4±213.4	2.9±9.3	0.006*
PEDT score	−1.1±2.6	−3.5±4.9	−0.25±1.4	0.003*
Erectile function	1.2±2.7	2.6±3.6	1.2±0.98	0.11
Orgasmic function	0.24±1.4	0.74±1	−0.12±1.4	0.076
Sexual desire	0.32±0.8	0.38±1.8	0.33±0.96	0.98
Intercourse satisfaction	0.28±1.4	1.8±3	−0.12±0.89	0.003*
Overall satisfaction	0.32±1.8	2.1±2.7	−0.5±0.98	<0.0001*
IIEF total score	2.4±6.4	7.7±10.1	0.8±3.4	0.004*

Data expressed as mean±SD. *P* values were calculated by one-way ANOVA. **Post hoc* tests (Bonferroni) show that significant differences between paroxetine with tamarind and placebo and between tamarind and placebo were not significant. IELT: Intravaginal ejaculation latency time, PEDT: Premature ejaculation diagnostic tool, IIEF: International Index of Erectile Function

Table 3: Comparison of adverse events occurring among study groups

Adverse events	Group			*P*
	Tamarind (*n*=25)	Paroxetine (*n*=23)	Placebo (*n*=24)	
Nausea	0	4 (17.3)	0	0.031
Drowsiness	0	6 (26.1)	1 (4.2)	0.014
Constipation	1 (4)	0	0	0.8
Reduced libido	0	2 (8.7)	0	0.32
Total adverse events	1 (4)	10 (43.5)	1 (4.2)	0.0002

Data expressed as *n* (%). *P* values calculated by Chi-square test

other studied variables were improved compared to placebo group. It is possible that low sample size decreases the power of our study to detect differences between groups. Also, in Iranian traditional medicine, tamarind seed powder was suggested for PE with no exact recommended dosage or time for its use. Hence, in the present study, we used tamarind seed powder at small dosage during 4 weeks and increase in dosage and time may be more effective than placebo on this outcome.

Four weeks' use of paroxetine in our study similar to other studies[33-35] shows improvements in IELT sexual satisfaction and other outcomes with more side effects than control group. A systematic review short report shows that a range of treatment options are available for patients presenting with PE. Pharmacological interventions, topical anesthetics, and behavioral therapies are useful approaches to PE management, but pharmacological and topical therapies are associated with some adverse effects.[12] Furthermore, there is limited evidence regarding the long-term safety and effectiveness of treatments and following cessation of many treatments their effects may be expected to end.[13] On the other hand, other therapies including acupuncture, yoga, Chinese medicine, and herbal medicine were assessed in other studies as alternative medicine in the management of PE.[16-21,36-38] However, because of verity and limited evidence-based information, the efficacy and safety of these approaches compared to placebo or other usual treatments are unclear. In the present study, for the first time, based on Iranian traditional medicine recommendation, small dose of tamarind seed powder as an alternative treatment to PE management was assessed and our findings were not different from placebo and were significantly less effective than paroxetine. However, as a new herbal product approach, additional research is required to eventually assess different doses and periodic use of tamarind seed powder alone or combined with other treatments options for the management of PE.

Conclusions

In conclusion, our study suggested that tamarind seed powder was not significantly different from placebo in the treatment of PE and also paroxetine as a routine treatment was better than tamarind seed powder. This randomized study is exploratory with no reported side effect for tamarind compared to paroxetine. So, the future researches can be design on higher dose of tamarind seed powder on a large number of patients with PE.

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Conflicts of interest

There are no conflicts of interest.

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