Comparison of Dapoxetine /Tadalafil and Paroxetine/Tadalafil Combination Therapies for the Treatment of the Premature Ejaculation: A Randomized Clinical Trial

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Purpose: The purpose of this study was to compare the effectiveness of Dapoxetine, and Paroxetine as well as Dapoxetine/Tadalafil and Paroxetine/Tadalafil combinational therapies, for the treatment of patients with premature ejaculation.

Materials and Methods: In this clinical trial study, 120 patients with premature ejaculation were randomly divided into 4 groups: The first group was treated with Paroxetine (Pa), while the second group received Dapoxetine(Da). The third group received Paroxetine combined with Tadalafil(PT) whereas the fourth group's treatment involved the use of Dapoxetine and Tadalafil(DT) for one month. In the next 2 and 4 weeks, the cases were evaluated in terms of ejaculation duration, frequency of intercourse per week, and drug side effects.

Results: The mean age of the Da, Pa, PT, DT groups was 32 ± 6.9, 32.4 ± 7.2, 31.6 ± 1.9, and 32.9 ± 7.7 years, respectively. There was a significant difference between the Da and DT groups (p = .029) in the ejaculation latency in the 4-week follow-up. In the two weeks follow-up, a significant difference was observed between DA and DT (p = 0.043), Pa and PT (p = 0.006), and Pa and DT groups (p = 0.004) in terms of ejaculation latency. Four weeks after the intervention, a significant difference was detected in the intercourse frequency of Da and PT groups (p =0.033), Pa and PT groups (p = 0.043), Pa and DT groups (p = 0.02), and Da and DT groups (p = 0.016).

Conclusion: Combination therapy (Tadalafil plus Paroxetine or Dapoxetine) was more effective in IELT (Intra ejaculation latency time) than mono-therapy especially in younger patients despite its slightly more side effects.

Keywords: dapoxetine; paroxetine; premature ejaculation; tadalafil; treatment

INTRODUCTION

The average time to reach orgasm in men is 4 minutes [(1,2)]. In most sources, premature ejaculation refers to cases in which ejaculation occurs in less than one minute from the onset of intercourse. Some others consider ejaculation sooner than two minutes as abnormal and premature ejaculation. It should be noted that this definition is limited to intercourses through the vagina [(3,4)].

According to the statistics, premature ejaculation affects more than one-third of men. The rate of premature ejaculation is 31% in the United States and 66% in Germany[(3)]. Extensive studies on the anatomy of animal nerves and neuropharmacology have concluded that different regions control ejaculation rate through neurotransmitters such as serotonin and dopamine[(5,6)].

Dapoxetine is one of the specific serotonin reuptake inhibitors (SSRIs) on the market that has no place in the treatment of depression. Thanks to its unique formulation and kinetics with rapid effect and short half-life, it could be applied in the treatment of premature ejaculation on-demand. Paroxetine has been also used in various studies to treat premature ejaculation[(7,8)]. The duration of erection seems to be one of the main concerns of patients with premature ejaculation[(9,10)]. PDE5 inhibitor (Tadalafil) is the gold standard first-line treatment for erectile dysfunction capable of prolonging the ejaculation duration[(11,12)]. However, some studies prefer single-drug therapy due to the high side effects of combination drugs[(6,13)].

MATERIALS AND METHODS

Study Population

In this parallel clinical trial study, 120 patients with premature ejaculation referring to the urology clinic in Imam Reza Hospital, Ardabil, Iran were selected. These patients were selected from those with the complaint of premature ejaculation. The subjects were married with the age range of 20-50. All the selected patients had IELT (Intra ejaculation latency time) of less than 2 minutes. They had sexual intercourse at least once a week. The sample size was calculated to be equal to 120 items using G * Power 3.1.9.2 software considering the alpha and study power values of 0.05 and 0.8 for each group and with an effect size of 0.7, respectively.

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Table 1. Comparison of ejaculation time and number of relationships per week (Sex Frequency in the studied groups at different times

Time	groups	ejaculation time	*P*-value	number of relationships per week (Sex Frequency)	*P*-value
Before the intervention	Dapoxetine	57.8 ± 34.2	0.9	2.04 ± 0.85	0.9
	Paroxetine	59.4 ± 32		2.08 ± 1	
	Dapoxetine + Tadalafil	56.1 ± 31		2 ± 0.8	
	Paroxetine + Tadalafil	54.6 ± 30.9		1.93 ± 0.8	
Two weeks after the intervention	Dapoxetine	166.7 ± 67.3	0.001	2.1 ± 0.8	0.036
	Paroxetine	146.4 ± 69.5		2.1 ± 1	
	Dapoxetine + Tadalafil	230 ± 112.6		2.63 ± 0.8	
	Paroxetine + Tadalafil	227.1 ± 90		2.64 ± 0.9	
Four weeks after the intervention	Dapoxetine	204.4 ± 82	0.007	2.2 ± 0.8	0.002
	Paroxetine	208.8 ± 65.1		2.2 ± 0.7	
	Dapoxetine + Tadalafil	269.9 ± 100.4		2.9 ± 0.9	
	Paroxetine + Tadalafil	259.3 ± 83.4		2.8 ± 0.9	

Patients were selected by simple sampling and entered into study groups by distributing cards in four colors each assigned to one drug group. The study addressed 4 groups and each group consisted of 30 people. These four colors were written on four separate papers and the papers were placed inside a black bag. The participants were asked to pick up one piece of paper.

Inclusion and exclusion criteria

Exclusion criteria were having an underlying disease including diabetes, heart disease, high blood pressure, thyroid disease, sexually transmitted diseases, psychiatric illnesses treated with any psychiatric medication, and erectile dysfunction. Patients who did not tolerate the side effects of drugs were also excluded from the study

Procedures

Data were collected using a designed checklist. No placebo was used in this study and all treatment groups were according to the guidelines for premature ejaculation treatment, thus no blinding was performed in this study. Patients were randomly divided into 4 groups:
All groups followed a one-month treatment period. The first group (control) received Dapoxetine 30 mg tablets (Shafa Pharmaceutical Company) orally one hour before sexual intercourse. The second group received Paroxetine 20 mg tablets (Tehran Shimi Company) orally once a day. The third group received Paroxetine 20 mg tablets (Tehran Shimi Company) orally once a day combined with Tadalafil 10 mg tablets (Rozdaro Pharmaceutical Company) orally one hour before sexual intercourse. The fourth group used Dapoxetine 30 mg tablets (Shafa Pharmaceutical Company) and 10 mg Tadalafil tablets (Rosedaro Pharmaceutical Company) orally one hour prior to sexual intercourse. Patients' information including their age, IELT, and intercourses frequency in a week were recorded in researcher-made checklists before treatment. Patients were contacted by the researcher for follow-up in the second and fourth weeks after treatment. The checklists including IELT, drug side effects (headache, hot flashes, sleep disturbance, nausea, vomiting, dizziness, and fatigue), and the number of intercourses per week were studied.

Evaluations

The conditions of the study were fully explained to the patients and they consciously signed a written consent form to participate in the study. Patients completely voluntarily took part in the study and they were assured that could leave the study at any time. Their information was strictly kept confidential and recorded without their name or address. The study procedure was approved by the Ethics committee of Ardabil University of medical sciences (NO: IR.ARUMS.REC.1398.315) with IRCT NO (20190528043747n1) and adhered to the tenets of the declaration of Helsinki.

Statistical Analysis

The collected data were encoded in SPSS software version 21 using descriptive-analytical statistical methods as number, percentage, and mean values. Various statistical tests such as ANOVA and Tukey's post hoc test were applied to compare the two groups while the chi-square test was employed to examine their relationship. Concerning the side effects, different drugs were separately analyzed at different times.

RESULTS

In this study, patients in the four groups did not significantly differ in terms of age ($P > .05$). The mean age of members of the Dapoxetine, Paroxetine, Paroxetine/Tadalafil, and Dapoxetine/Tadalafil groups was 32 ± 6.9, 32.4 ± 7.2, 31.1 ± 6.9, and 32.9 ± 7.7 years, respectively. The four treatment regimes caused a significantly different effect on the ejaculation latency. The latency time for first, second, third, and fourth groups after 4-week treatment were 204.4 ± 82, 208.8 ± 65.1, 269.9 ± 100.4, and 259.3 ± 83.4 s, respectively.
Table 1. Comparison of ejaculation time (IELT) and number of sexual intercourses per week
Based on Table 1, two and four weeks after the intervention, the latency time increased in all groups, however, the longest ejaculation latency was observed in the third group (Dapoxetine combined with Tadalafil). Using the Tukey test for the dual study of the groups four weeks after the intervention, a significant difference was found between Da and DT groups ($P = .029$), while the other groups did not show a significant difference. Even two-week treatment by Tadalafil in these groups significantly prolonged the latency time (Comparing Da with DT ($P = .043$), Pa with PT ($P = .006$), and Pa with DT ($P = .004$)). The effects of Dapoxetine, Paroxetine, Dapoxetine/Tadalafil, and Paroxetine/Tadalafilon on premature ejaculation were different in terms of the weekly frequency of intercourse.
Regarding the weekly frequency of intercourse, there was a significant difference between the groups in the two-week and four-week follow-ups. Two weeks after the intervention, the mean frequency of intercourse per week was slightly higher in the PT group compared to

Table 2. The testis weight of mice in different treated groups and control after treatment

complications	First group dapoxetine		second group paroxetine		Third group dapoxetine+tadalafil		Fourth group paroxetine+tadalafil	
	two weeks after treatment	four weeks after treatment	two weeks after treatment	four weeks after treatment	two weeks after treatment	four weeks after treatment	two weeks after treatment	four weeks after treatment
Headache	11.1	11.1	12	16	38	37	35.7	35.7
Flushing	0	0	0	0	18.5	18.5	17.9	17.9
sleep disorder	7.4	11.1	12	16	14.8	44.4	17.9	42.9
nausea	11.1	11.1	16	12	22.2	25.9	28.6	32.1
Vomit	0	0	0	8	3.7	3.7	3.6	0
Vertigo	7.4	7.4	0	0	3.7	3.7	14.3	10.7
Fatigue	7.4	7.4	0	0	0	0	0	3.6

the others. Four weeks after the intervention, groups treated with Tadalafil plus arms exhibited statistically significant more intercourse frequencies, although the mean frequency of intercourses in the DT and PT groups was almost the same. Using the Tukey test, the results of binary comparison of the groups in the four-week follow-ups showed significant differences among the groups regarding intercourse frequency (Da and PT (P =.033), Pa and PT (P = .043), Pa and DT (P = .022), Da and DT (P = .016)).

Table 2. Comparison of the drugs in terms of complications two and four weeks post-intervention.

The mentioned treatments caused significantly different side effects. According to **Table 2**, two weeks after the intervention, there was a significant difference in complications such as headache and hot flashes, but no significant difference was detected between the groups in terms of other side effects. PT and DT groups with 10 cases of headache and 5 cases of hot flashes had the most complications.

The groups were significantly different in terms of hot flashes and sleep problems after four weeks of intervention. Regarding hot flashes, 5 people in each of the PT and DT groups had the most complications. Concerning sleep disorders, the most complications were in the PT and DT groups with 12 people in each group.

The effects of dapoxetine, paroxetine, dapoxetine/tadalafil, and paroxetine/tadalafil in the treatment of patients with early ejaculation are significantly different based on the patients' age.

Table 3. Comparison of IELT medicinal based on the age group

According to Table 3, after two and four weeks of the medical intervention in the age groups of 20-30, there was a significant difference between the drug groups in terms of ejaculation latency. Two and four weeks post-intervention, the combined DT group had a longer IELT duration with average values of 240.5 ± 117 and 286.112 ± 2.7 s, which was significantly different from the other groups.

No significant difference was observed between the groups in the age group of 31-40 and 41-50 in terms of (IELT) two and four weeks after the intervention as compared to the condition before the intervention.

DISCUSSION

Our study showed that adding Tadalafil to Paroxetine or Dapoxetine fortifies ejaculation latency time. Zhang X et al. compared the combination therapy of sildenafil and sertraline versus sertraline monotherapy for the treatment of premature ejaculation. They showed that combination therapy was more efficient than mono-therapy with fewer side effects[14]. However, in our study combination therapy exhibited a mild increment of headache and hot flashes.

Premature ejaculation has a prevalence of 20-30 % in the male population. Tadalafil may be efficient in improving (IELT) even in combination with the pause-squeeze technique or glandular local anesthesia. Dell'Atti L et al. compared Tadalafil with local anesthetics and reported the efficacy and tolerability of Tadalafil in premature ejaculation[15].

Our study did not show a considerable difference in efficacy or side effects of Dapoxetine and Paroxetine. However, Jern P. et al. reported a higher rate of discontinuation for Dapoxetine compared to Paroxetine. Paroxetine was more effective and tolerable than Dapoxetine[16].

Moudi E et al. compared Tadalafil plus Paroxetine with Paroxetine only in the treatment of premature ejaculation. They showed that Tadalafil could moderately increase intravaginal ejaculation latency time (IELT) and might be used to treat premature ejaculation in combination with Paroxetine[1]. This confirms our results that a combination of SSRI and PDE5 inhibitors could outperform monotherapy for the treatment of premature ejaculation. In the study of Muhammad Abu al-Hamd, the combination of Sildenafil plus Dapoxetine led to the best response[17].

In a meta-analysis, Martyn-St James M et al. reported that although monotherapy by SSRI and PDE-5 inhibitors did not cause much difference in latency time, their combination therapy can make a significant difference [18].

ANOVA test was applied to compare the IELT of the four groups. The results showed that before the intervention, the groups were the same in terms of ejaculation time. Two and four weeks later, dapoxetine/Tadalafil and paroxetine/Tadalafil groups exhibited significantly longer ejaculation latency time than the two groups of dapoxetine and paroxetine groups with the longest belonging to the dapoxetine/Tadalafil group. These results indicate that combination therapies of Dapoxetine/Tadalafilor and Paroxetine/Tadalafil had more effect on increasing ejaculation latency time in patients with premature ejaculation rather than single Dapoxetine or Paroxetine.

In a clinical trial by McMahon et al., the use of Dapoxetine 1 to 2 hours before intercourse at doses of 30 mg and 60 mg enhanced the ejaculation latency by 2.5 and 3 times, respectively[19]. Pryor et al. also reported that

Table 3. The mean serum testosterone, FSH and LH levels in different treated groups and control after treatment.

time to study	drug group	age group of 20-30	*P*-value	age group 31-40	*P*-value	age group 41-50	*P*-value
before the intervention	dapoxetine	53.07 ± 23.4	0.7	61.4 ± 43.2	0.9	65 ± 48.2	0.9
	paroxetine	58.8 ± 32.94	54.4 ± 34.9	69 ± 29.2			
	paroxetine + tadalafil	47.1 ± 24.1	63 ± 35.2	60 ± 42.4			
	dapoxetine + tadalafil	49.6 ± 23.2	51.7 ± 31.02	81 ± 41.9			
two weeks after the intervention	dapoxetine	161.5 ± 66.6	0.009	174.6 ± 78.02	0.7	160 ± 34.6	0.3
	paroxetine	125 ± 54	142.5 ± 55	204 ± 100.4			
	paroxetine + tadalafil	210 ± 93.4	240 ± 93.8	255 ± 75.5			
	dapoxetine + tadalafil	240 ± 117.5	176.7 ± 77.1	300 ± 127.3			
four weeks after the intervention	dapoxetine	184.6 ± 71.3	0.006	212.7 ± 94.3	0.14	260 ± 69.3	0.5
	paroxetine	185 ± 40.1	180 ± 45.4	312 ± 26.8			
	paroxetine + tadalafil	235.7 ± 76.1	270 ± 90.6	315 ± 75.5			
	dapoxetine + tadalafil	286.2 ± 112.7	213.3 ± 74.2	324 ± 68.4			

receiving Dapoxetine 1 to 2 hours before intercourse caused more control over ejaculation, reduced stress, and increased satisfaction[20]. Dapoxetine was effective in both sustained and acquired premature ejaculation[21-23]. In 2018, Li et al. conducted a meta-analysis study addressing the effects of Dapoxetine on the treatment of premature ejaculation, they concluded that doses of 30 mg and 60 mg were more effective than placebo for ejaculation latency time[24].

In some studies, Paroxetine incremented mean IELT from 0-1 minute to an average of 4.5 minutes after 4-week treatment which was raised to 5.5 minutes after another 4-week therapy[25-27].

On the contrary, some studies reported no difference between the combined treatment of Paroxetine-Tadalafil compared with Paroxetine. They showed that the mean IELT after 3 months and even 6-month of treatment were not significantly different[28-30]. So it seems that combination therapy has not been regarded as a standard treatment for premature ejaculation yet.

However, Polat EC et al. showed that the use of combination therapy with serotonin re-uptake inhibitors (SSRI) and phosphodiesterase type 5 inhibitors (PDE5-inhibitors) (combination therapy of Paroxetine + Tadalafil) can lead to a significantly better effect on increasing IELT than the single use of these drugs[31]. In the present study, the combined groups exhibited a greater increase in ejaculation latency time than the single therapy groups. Concerning the frequency of intercourse per week, there was no difference between the groups. Two and four weeks after the intervention, however, the frequency of intercourses significantly increased. The Dapoxetine/Tadalafil and Paroxetine/Tadalafil groups sowed almost at the same conditions in terms of the average frequency of intercourses per week; they exhibited, however, significantly higher intercourse frequency compared to Dapoxetine and Paroxetine groups. The combination therapy groups had longer ejaculation times, leading to more sexual satisfaction and desire compared to single drug groups which raised the intercourse frequency[32,33].

Side effects of Dapoxetine include nausea and vomiting, diarrhea, dizziness, headache, and insomnia. Side effects of Paroxetine have been reported as the inability to ejaculate, and a decreased libido[31,34]. In this study, common side effects were headaches and hot flashes that were more common in Tadalafil plus groups.

Other side effects were sleep disorders, nausea, vomiting, dizziness, and fatigue. The results indicated that two weeks after the intervention, there was a significant difference between the groups in terms of headache and hot flashes. However, no significant difference was found between the groups concerning other complications. These side effects were greater in the Dapoxetine/Tadalafil and Paroxetine/Tadalafil groups than the Dapoxetine and Paroxetine groups. After 4 weeks, hot flashes and sleep problems were significantly more common.

Younger patients showed better responses to premature ejaculation treatment. In the age group of 20-30, Dapoxetine/Tadalafil had the greatest effect on the (IELT), but there was no significant difference in the (IELT) after the intervention compared to the start of the intervention the age groups of 31-40 and 41-50.

According to the results of this study, more studies are recommended on the treatment of premature ejaculation with the combination therapy of dapoxetine/tadalafil and paroxetine/ tadalafil with a larger sample size and longer follow-up period.

The sample size of this study was about 26 people in each group. It seems that more sample size could raise the accuracy of the results. Another limitation of the present study was the lack of control over the correct use of prescribed drugs during treatment, which may disturb the results. Satisfaction of individuals who can determine the outcome of drug tolerance and the effect of treatment was not examined in this study, which is another limitation of this study.

CONCLUSIONS

Combination therapy (Tadalafilpl us Paroxetine or Dapoxetine) is more effective in IELT than monotherapy especially in younger patients although it may cause slightly more side effects.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

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