ERECTILE DYSFUNCTION

A Small Group Randomized Double-Blind Placebo-Controlled Study to Evaluate the Efficacy of Daily Pentoxifylline in the Management of Patients With Erectile Dysfunction with Suboptimal Treatment Response to Sildenafil

Yu Xi Terence Law, BSc (Hons), MBBS, MRCS,[1] Bee Choo Tai, MSc, PhD, Cstat,[2,3] Yi Quan Tan, MBBS, MRCS,[1] Raman Nee Mani Lata, MBBS,[1] and King Chien Joe Lee, MBBS, MRCS, MMed (Surg), FAMS (Urology)[1]

ABSTRACT

Introduction: Several studies have reaffirmed the use of regular pentoxifylline therapy in increasing the penile brachial pressure index in men affected by erectile dysfunction when compared to placebo.

Aim: The aim of this study was to evaluate the efficacy of pentoxifylline as an adjunctive treatment for patients with erectile dysfunction.

Methods: This study was a single center, prospective, randomized, double-blind, placebo-controlled trial. Subjects were recruited between April 2014 and November 2016 from the National University Hospital, Singapore. The combination therapy group was given pentoxifylline 400 mg thrice daily orally and the monotherapy group was given placebo capsules thrice daily orally. Both groups continued their on-demand 100 mg sildenafil. The treatment duration was 8 weeks. Efficacy was measured via the International Index of Erectile Function (IIEF-5) questionnaire at the eighth week. Differences in mean IIEF-5 score and the domains of the IIEF at 8 weeks between the 2 treatment groups were compared using independent sample *t*-test.

Main Outcome Measure: Baseline IIEF-5 and the IIEF-15 score vs post-therapy IIEF-5 and the IIEF-15 score.

Results: 50 patients were randomized into 2 groups. Patients in the 2 groups were comparable in terms of the demographic and clinical characteristics, comorbidities, and baseline IIEF-5 scores. The mean IIEF-5 score post-therapy of the combination therapy group vs the monotherapy group was 14.11 and 14.87, respectively. There was no significant difference between the outcomes of these 2 groups (unadjusted mean difference -0.76; 95% CI -4.01 to 2.49; $P = .641$) and the outcomes are the same even after adjusting for baseline IIEF-5 scores. There was a significant improvement in the "overall satisfaction" portion of the IIEF score for the combination therapy group as compared to the monotherapy group (unadjusted mean difference 0.12; 95% CI -1.49 to 1.25) and even after adjustment for baseline scores (adjusted mean difference 1.11; 95% CI 0.10 to 2.12; $P = .032$) the improvement is significant.

Conclusion: Our trial suggests that the use of combination therapy does not improve the management of patients compared to monotherapy. **Law YXT, Tai BC, Tan YQ et al. A Small Group Randomized Double-Blind Placebo-Controlled Study to Evaluate the Efficacy of Daily Pentoxifylline in the Management of Patients With Erectile Dysfunction with Suboptimal Treatment Response to Sildenafil. Sex Med 2019;8:14–20.**

Key Words: Pentoxifylline; Erectile Dysfunction; Placebo-Controlled Trial; Phosphodiesterase-5 Inhibitor

Received March 3, 2019. Accepted August 19, 2019.

[1]Department of Urology, National University Hospital, National University Health System, Singapore;

[2]Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore;

[3]Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore

https://doi.org/10.1016/j.esxm.2019.08.012

INTRODUCTION

Erectile dysfunction (ED) refers to an inability to achieve or maintain an erection enough for satisfactory sexual performance.[1] The Global Study of Sexual Attitudes and Behaviours showed that, in a population of 13,618 men aged between 40 and 80 years, 10% of them has erectile dysfunction.[2] Although large multicenter clinical trials have shown fair efficacy and tolerability of oral phosphodiesterase-5 (PDE-5) inhibitors in ED with various etiologies and a broad range of severity,[3–5] 30–35% of patients fail to respond.[6] Patients who fail to respond to PDE-5 will require more invasive second or third-line treatments, such as intracavernosal injection of vasodilators and surgical implantation of penile prostheses.[7]

Pentoxifylline is a nonspecific PDE inhibitor and a methyl xanthine derivative used especially for chronic occlusive arterial disease.[8] It improves capillary blood flow by increasing erythrocyte flexibility and inhibiting thrombocyte aggregation and has been used for regulating blood circulation in patients with cerebral or peripheral vascular diseases.[9] Atherosclerosis with resultant compromised blood perfusion is a common pathophysiology shared by vasculogenic ED and peripheral vascular disease. Several studies have reaffirmed the use of regular pentoxifylline therapy in increasing the penile brachial pressure index in men affected by ED when compared to placebo.[10,11] We postulate that daily consumption of pentoxifylline based on the dosage used to treat peripheral vascular disease would have a positive effect on erectile function and penile blood flow.

The primary objective of this study was to evaluate the efficacy of pentoxifylline as an adjunctive treatment for patients with ED. It was used in combination with on-demand 100 mg sildenafil in the treatment of ED.[12]

METHODS

Study Design

The study was a single center, prospective, randomized, double-blind, placebo-controlled trial comparing monotherapy on-demand 100 mg sildenafil only (S only) vs combination therapy of sildenafil with pentoxifylline (S+P). Subjects were recruited between April 2014 and November 2016 from the National University Hospital, Singapore. Our treatment duration was optimal at 8 weeks. Patients are evaluated using the International Index of Erectile Function (IIEF).[13] The trial study was approved by our institutional review board, NHG DSRB Ref. no. 2012/02236.

Patient Selections

Male patients with ED and suboptimal responses for the IIEF[13] score $\leq$21 to on-demand 100 mg sildenafil treatment were recruited. Inclusion criteria were as follows: over 21 years of age, in a steady relationship with the same female partner, and only on sildenafil (100 mg) for ED during the past 3 months. Patients should also able to demonstrate proper usage of sildenafil (100 mg), which includes taking it on empty stomach, to take 1 hour before copulation, and attempted at least 6 times.[14]

Exclusion criteria were as follows: history of spinal injury or neurological disorders, history of pelvic or genital trauma or penile implant or clinically significant penile deformity like Peyronie's disease, HIV infection, severe psychiatric disease, untreated endocrine disease, including uncontrolled hypertension of systolic blood pressure $\geq$170 and/or diastolic blood pressure $\geq$100 mmHg, uncontrolled diabetes (HbA1c $\geq$8.1), cardiac arrhythmias or unstable angina or congestive heart failure within the past 6 months, history of myocardial infarction, coronary artery bypass grafting, or angioplasty within the past 3 months, history of drug or alcohol abuse within the past 6 months, had undergone radical prostatectomy or pelvic radiotherapy, significant renal or hepatobiliary disease, retinitis pigmentosa, and/or currently on medication like nitrates, cancer chemotherapy, anti-androgens, warfarin, heparin, ketorolac, and theophylline.

All patients provided written informed consent for involvement in the study.

Randomization

The randomization list was computer generated, with equal allocation to the 2 treatment arms. ED in patients with diabetes mellitus can be contributed by the neurogenic component, which may result in poor response to PDE-5 inhibitor,[15] as such, stratified randomization according to the presence of diabetes mellitus was fully implemented.

Study Treatment

The intervention group (S+P) were given pentoxifylline (400 mg) thrice daily orally for 8 weeks and the control group (S only) were given placebo capsules thrice times daily orally for 8 weeks. Both groups continue on-demand 100 mg sildenafil. Both groups were advised not to take any herbal or other medications for ED. The pentoxifylline and placebo were manufactured in Malaysia by CCM Pharmaceuticals Pte Ltd, whereas the sildenafil was manufactured in Ireland by Pfizer.

The trial drug was dispensed by the study coordinator in pill bottles containing 168 capsules and packaged in a double-blind manner. The active and placebo tablets were identical in terms of appearance and taste. The treatment code was kept under the custody of the protocol administrator and provisions were made for the code to be broken in the event of an emergency when it was critical to obtain precise knowledge of the treatment that a patient received.

Sample Size

Ozdal et al[12] reported a difference in mean IIEF of almost 4 points between patients allocated to receive S only and S+P. As our study targeted patients with more severe ED having

suboptimal response to S therapy, the sample size for this trial was calculated based on the assumption that there will be a clinically significant improvement of 3 points in the IIEF-5 score in the intervention (S+P) arm as compared to the control (S only) arm. Assuming a mean IIEF-5 score of 13 for the control group (S) at 8 weeks, with a common SD of 8, a minimum sample size of 224 (ie, 112 per group) would be required based on a power of 80% and a level of significance of 5%. Accounting for approximately 10% attrition, we would need to recruit a total of 250 subjects.

Study Assessment, Follow-Up, and End Point

The original IIEF instrument consisting of 15 items and 5 domains was used. The 5 domains include erectile function (EF), orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction (OS).

The abridged version of the IIEF (IIEF-5), comprising 5 items of the IIEF, which focused primarily on EF and intercourse satisfaction, is the diagnostic tool to identify the presence and severity of ED in clinical settings. Possible scores of the IIEF-5 range from 1−25. In this protocol, the IIEF-5 was defined as the primary end point of interest.

By using both the IIEF-5 and the IIEF-15, we aim to not only to assess the effects on pentoxifylline on EF, but also its possible effects on other aspects of sexual function.

Both groups returned for follow-up evaluation of the IIEF at week 8. During this visit, the patient's diary was collected. The drug accountability and adverse events (AEs) were also recorded.

Statistical Methods

Differences in mean IIEF-5 score and the domains of the IIEF at 8 weeks between the 2 treatment groups were compared using independent sample *t*-test. *P* values of $< .05$ is considered to be significant. The analysis of covariance was used to adjust for the baseline IIEF-5 or domain scores. All statistical evaluations were generated using STATA version 14 assuming a 2-sided test at the conventional 5% level of significance. The statistical analyses were performed according to the principle of intention-to-treat.

RESULTS

A total of 58 patients were randomized to receive either S+P ($n = 31$) or S only ($n = 27$) between April 2014 and November 2016. The independent Data Monitoring Committee reviewed the preliminary results after the recruitment of 58 patients and recommended that the trial steering group should consider closing the trial to new entrants as the preliminary data do not suggest significant improvements. Of these 58, 7 patients (4 S+P, 3 S only) withdrew from the trial (4 due to adverse effect and 3 due to change of mind), and 1 patient in S did not return for the 8-week follow-up (Figure 1). 50 patients (27 S P, 23 S only) remained after exclusion, whose outcomes were available for an intention-to-treat analysis.

Patient Characteristics

Table 1 shows that the patients in the intervention group (S+P) and control group (S only) were comparable in terms of the demographic and clinical characteristics. Overall, the mean age was 59.7 years (range from 29.2 to 80.6 years). For the etiology of ED, about half the patients had diabetes mellitus, whereas more than two-thirds had hypertension, and 59% of them had hyperlipidemia. Both groups had similar mean baseline IIEF-5 score of 13 with a SD of 5.

Treatment Compliance

In total, only 16 of 58 patients (28%; 9 patients in S+P and 7 in S only) were fully compliant to the respective treatment regime by consuming all the tablets. Noncompliance is only considered when >30 capsules of 168 caplets dispensed are not consumed. 39 of 58 patients (67%) are compliant and only 19 patients (11 patients in S+P and 8 patients in S only) had a

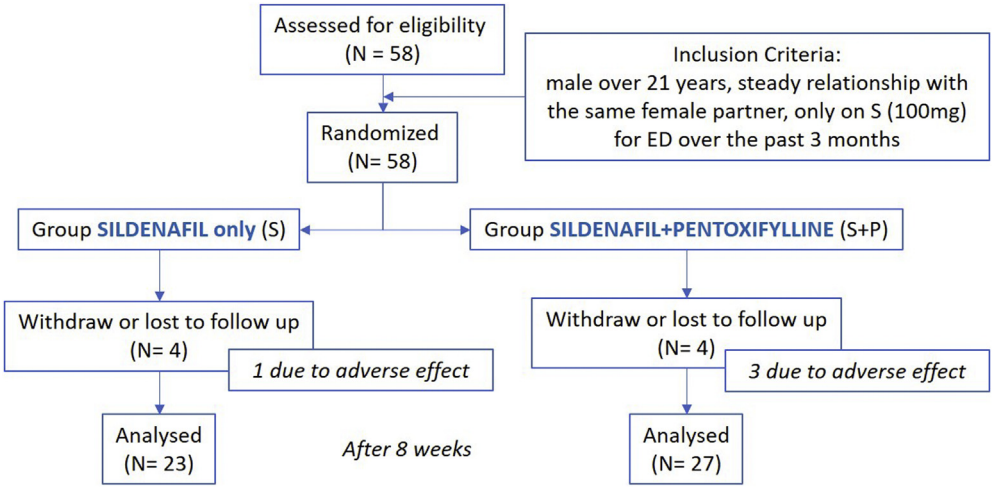

Figure 1. Trial profile.

Table 1. Baseline characteristics by treatment

Characteristic	S+P (n = 31)	S (n = 27)	All patients (n = 58)
Age, years			
Mean	59.3	60.1	59.7
Range	29.2–80.6	43.8–75.9	29.2–80.6
Diabetes mellitus (%)	15 (48)	12 (44)	27 (47)
Hypertension (%)	20 (65)	21 (78)	41 (71)
Hyperlipidemia (%)	16 (52)	18 (67)	34 (59)
Ischemic heart disease (%)	5 (16)	4 (15)	9 (16)
Stroke (%)	1 (3)	0 (0)	1 (2)
PVD (%)	1 (3)	0 (0)	1 (2)
Anti-DM medication (%)	15 (48)	12 (44)	27 (47)
Anti-hypertensive medication (%)	18 (58)	20 (74)	38 (66)
Anti-lipid medication (%)	18 (58)	19 (70)	37 (64)
Anti-platelet medication (%)	8 (26)	7 (26)	15 (26)
Mean SBP (SD)	138.0 (16.1)	146.0 (15.8)	141.6 (16.3)
Mean DBP (SD)	78.9 (7.7)	82.5 (9.0)	80.5 (8.5)
Mean pulse rate (SD)	74.3 (12.2)	70.0 (13.3)	72.3 (12.8)
Mean IIEF-5 (SD)	12.8 (5.2)	13.1 (5.0)	12.9 (5.1)
Mean EF (SD)	15.5 (6.3)	15.9 (5.9)	15.7 (6.0)
Mean OF (SD)	6.0 (2.2)	6.1 (2.5)	6.1 (2.3)
Mean sexual desire (SD)	6.0 (1.3)	6.0 (0.8)	6.0 (1.1)
Mean IS (SD)	6.7 (2.7)	7.0 (2.7)	6.9 (2.7)
Mean OS (SD)	5.6 (2.3)	6.6 (2.0)	6.1 (2.2)

DBP = diastolic blood pressure; DM = diabetes mellitus; EF = erectile function; IIEF5 = International Index of Erectile Function 5 question; IS = intercourse satisfaction; OF = orgasmic function; OS = overall satisfaction; PVD = provoked vestibulodynia; S = sildenafil; S+P = sildenafil with pentoxifylline; SBP = systolic blood pressure.

balance of >30 of 168 caplets dispensed (Figure 2). Of these 19, the reason for noncompliance for 7 (5 S+P, 2 S only) was due to AEs and other reasons were forgetfulness for 4, oversea travels for 3, no improvement for 2, taking antibiotics for 1, fasting for 1, and self-reduced medication for 1. Overall, there is no significant difference in the compliance rate between the intervention group (S+P) and the control group (S only).

AEs

A total of 15 AEs were reported in 10 patients (7 S+P, 3 S only; risk ratio of S+P vs S only: 1.96; 95% CI 0.56–6.82; P = .275). 4 patients in the S+P group reported at least 2 events. The AEs reported were gastrointestinal (abdominal discomfort, abdominal distention, abdominal bloatedness, bleeding from piles, change in bowel habit, and nausea) in 6 patients (4 S+P, 2 S only), neurological (fatigue, giddiness, headache, and lethargy) in 5 patients (4 S+P, 1 S only), musculoskeletal (bilateral leg swelling and joint pain at fingers) in 2 patients (both S+P), and dermatological (pruritus and rash) in 2 patients (both S+P). The duration of AEs lasted between 2 and 56 days. A summary of the AEs is displayed in Table 2. 4 (3 S+P, 1 S only) of these patients due to AEs eventually withdrew from the study (Figure 1).

Primary and Secondary Outcomes

The mean IIEF-5 score of S+P and S only pretreatment were 12.8 and 13.1, whereas post-treatment were 14.11 and 14.87, respectively. Thus, the unadjusted difference in mean IIEF-5 score at 8 weeks comparing S+P vs S only was -0.76 (95% CI -4.01 to 2.49; P = .641). The result was not materially altered even after adjusting for the baseline IIEF-5 score (adjusted mean difference -0.35; P = .673; Table 3 and Figure 3). Of note is the OS, which suggested a significance difference in score between the 2 treatments (unadjusted mean difference 0.12; 95% CI -1.49 to 1.25), after adjustment for baseline score (adjusted mean difference 1.11; 95% CI 0.10 to 2.12; P = .032).

DISCUSSION

Pentoxifylline is a methyl xanthine derivative traditionally used for chronic occlusive arterial disease, including intermittent claudication.[8] It decreases blood viscosity, improves erythrocyte flexibility, and increases microcirculatory flow and the tissue oxygen concentration. Pentoxifylline is a nonspecific PDE inhibitor that potentiate the effects of endogenous prostacyclin, hence increasing cyclic adenosine monophosphate levels in red blood cells, platelets, and arterial wall cells.[8] In view of this property, pentoxifylline has been explored in the treatment of ED. The current evidence on pentoxifylline use (either sole or adjunctive) in the treatment of ED is mixed.

More recent studies have shown results of better efficacy with combination therapy as opposed to monotherapy with PDE-5 inhibitors.[12,16] In 2007, a pilot study by Ozdal et al[12] showed that although the mean IIEF score was higher after both S-only treatment and combination treatment (S+P) compared to pre-treatment scores, the increase in the IIEF score was higher in the combination therapy group by 4 (P < .001). In this pilot study, 68 patients received S only treatment for 4 weeks and were subjected to the IIEF questionnaire and a washout period of 4 weeks. Subsequently, the patients start on the S+P combination therapy for another 4 weeks and the IIEF questionnaire was performed again. The lack of randomization and placebo in the study may have led to bias and confounding.

Our study is the first randomized, controlled-trial, with a placebo control. This randomized, placebo-controlled study was intended to verify the Ozdal et al[12] study. Ozdal et al[12] reported a difference in the mean IIEF of almost 4 points between patients allocated to receive S only or S+P. At the time of closure, our trial did not manage to achieve the targeted sample size of 250

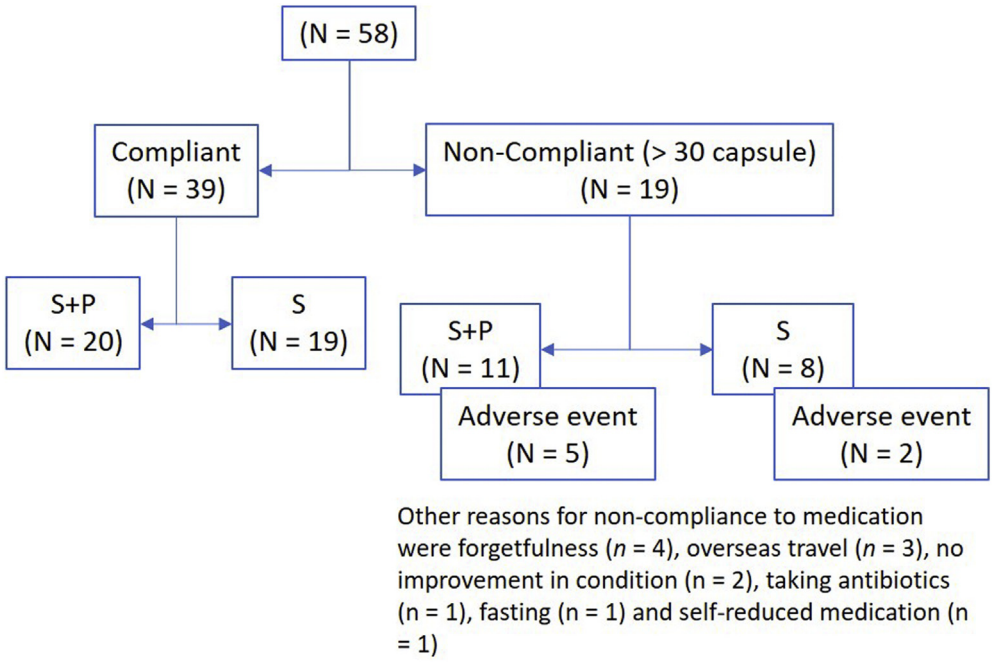

Figure 2. Compliance chart.

patients. However, our trial size of 50 patients was comparable to the Ozdal et al[12] study size of 68 patients.

Also in the Ozdal et al[12] study, only vasculogenic patients are recruited, but we included both vasculogenic and neurogenic patients. We performed stratified randomization of the patients with diabetes (predominantly neurogenic cause) in our study to prevent bias and confounding findings. It is noted that in the Ozdal et al[12] study, the patients had a minimum of 100 mg sildenafil per week, but for our study we did not capture the number of times patients have the on-demand 100 mg sildenafil.

Our study showed no difference in terms of the IIEF-5 scores obtained at 8 weeks post-treatment between the 2 regimes (S+P combination therapy vs with S only treatment). Interestingly, we saw significant improvement in OS (mean difference 1.11; 95% CI 0.10−2.12; $P = .032$). This significant improvement in OS but not in other domains may suggest other possible aspects of sexual function not clearly evaluated in the IIEF and, thus suggesting pentoxifylline improves aspect of ED not fully evaluated by the IIEF.

In a more recent randomized prospective trial by Kumar et al[16] involving 237 men with ED, patients who received tadalafil/pentoxifylline combination therapy had statistically significant improvements in the IIEF scores after 8 weeks as compared to those who took single agent tadalafil. Patients with severe ED in particular also experienced much greater improvements in EF with combination therapy.[16] Compared to our trial, the significant improvement in ED with combination therapy may be due to tadalafil's longer half-life (17.50 hours) compared to sildenafil (4−5 hours), but more randomized studies will be required to review this.

Table 2. Adverse events by treatment

Event	S+P	S	*P* value
Gastrointestinal	4	2	.678
Neurological	4	1	.362
Musculoskeletal	2	0	.495
Dermatological	2	0	.495

S = sildenafil; S+P = sildenafil with pentoxifylline.

In terms of the incidence of AEs between the 2 treatment arms, there were no significant differences.[12,16]

Our trial reflected a relative high rate of noncompliance. 33% of the trial patients had a balance of >30 of 168 caplets dispensed. So far, only our study has demonstrated the compliance issues associated with using pentoxifylline as a secondary drug to augment PDE5 inhibitors. Our high noncompliance rate may be explained by frequent drug dosing (1 tablet 3 times daily for 8 weeks). There was otherwise no significant difference in the compliance rate between the intervention group (S+P) and the control group (S only). In addition, in the Ozdal et al[12] study, the treatment period was only 4 weeks, whereas, in our study, our treatment period was double of that used in the Ozdal et al[12] study, hence the high noncompliance rate was not a contributor for the noneffectiveness of the S+P combination treatment. In addition, regrettably, as compliance was not analyzed in other studies, we were unable to compare our findings in this aspect with available studies.[10,12,16,17]

A key limitation of this trial was not achieving the desired sample size, but, nevertheless, this is the first prospective, randomized, double-blind, placebo-controlled trial reviewing the efficacy of combination therapy of S+P.

Table 3. Mean (SD) of IIEF domains and IIEF-5 at 8 weeks

Domain	S+P	S	Unadjusted difference (S+P) − S (95% CI)	Adjusted* difference (S+P) − S (95% CI)	*P* value*
IIEF-5	14.11 (5.83)	14.87 (5.55)	−0.76 (−4.01 to 2.49)	−0.35 (−2.00 to 1.31)	.673
EF	17.33 (6.96)	18.43 (6.71)	−1.10 (−5.01 to 2.81)	−0.66 (−2.81 to 1.49)	.539
OF	6.59 (2.15)	6.83 (2.42)	−0.23 (−1.54 to 1.07)	−0.15 (−1.09 to 0.78)	.746
SD	6.04 (1.19)	6.26 (1.45)	−0.22 (−0.98 to 0.53)	−0.15 (−0.81 to 0.50)	.637
IS	6.88 (1.95)	6.83 (2.85)	0.06 (−1.33 to 1.45)	0.47 (−0.41 to 1.35)	.289
OS	6.56 (2.42)	6.43 (2.39)	0.12 (−1.49 to 1.25)	1.11 (0.10 to 2.12)	.032

P value calculated using independent sample *t*-test.
EF = erectile function; IIEF5 = International Index of Erectile Function 5 question; IS = intercourse satisfaction; OF = orgasmic function; OS = overall satisfaction; S = sildenafil; S+P = sildenafil with pentoxifylline; SD = sexual desire.
*One patient in S+P with missing IS at week 8, adjusted for baseline score.

CONCLUSION

Our trial suggests that there is no role for pharmacological augmentation using pentoxifylline in patients who fail PDE-5 inhibitor. Overall, there was no difference with respect to the incidence of AEs between the 2 treatment arms.

ACKNOWLEDGMENT

The authors would like to thank the Data Monitoring Committee for their assistance to ensure data quality and integrity

Correspondence Author: Yu Xi Terence Law, BSc, National University Hospital, National University Health System, Department of Urology, 1E Kent Ridge Road, NUHS Tower Block, Level 8, Singapore 119228, Singapore. Tel: +65 6772 2002; Fax: +65 6694 0581; E-mail: terencelaw83@gmail.com

Conflict of Interest: The authors report no conflicts of interest.

Funding: National University Health System Investigational Medical Unit Award. This study is funded by the National University Health System Investigational Medical Unit Award. The sponsor is an institutional body set up to promote research in investigational medicine and experimental therapeutics. The sponsor had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or decision to submit the report for publication. During the study, the patients only paid for the on-demand sildenafil, otherwise the costs of pentoxifylline or placebo were covered by the study.

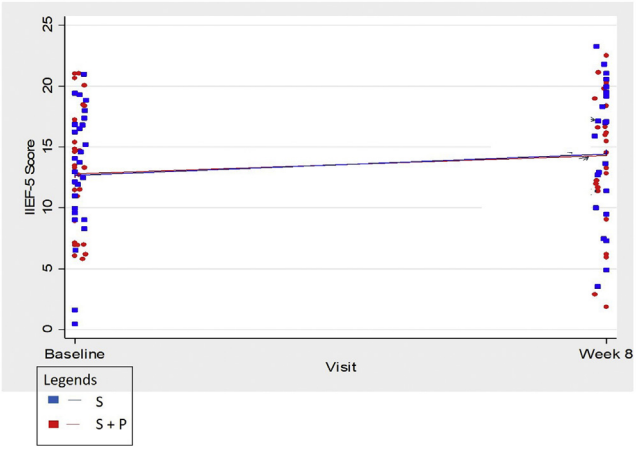

Figure 3. IIEF-5 score at baseline and week 8 by treatment.

STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design
King Chien Joe Lee

(b) Acquisition of Data
King Chien Joe Lee; Yi Quan Tan; Raman Nee Mani Lata

(c) Analysis and Interpretation of Data
King Chien Joe Lee; Bee Choo Tai; Yu Xi Terence Law

Category 2

(a) Drafting the Article
Yu Xi Terence Law; Bee Choo Tai; Yi Quan Tan

(b) Revising It for Intellectual Content
Yu Xi Terence Law; Bee Choo Tai; King Chien Joe Lee

Category 3

(a) Final Approval of the Completed Article
King Chien Joe Lee

REFERENCES

1. McCabe MP, Sharlip ID, Atalla E, et al. Definitions of sexual dysfunctions in women and men: A consensus statement from the Fourth International Consultation on Sexual Medicine 2015. **J Sex Med 2016;13:135-143.**
2. Nicolosi A, Laumann EO, Glasser DB, et al. Sexual behavior and sexual dysfunctions after age 40: The global study of sexual attitudes and behaviors. **Urology 2004;64:991-997.**
3. Goldstein I, Lue TF, Padma-Nathan H, et al. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. **N Engl J Med 1998;338:1397-1404.**
4. Tan HM, Moh CL, Mendoza JB, et al. Asian sildenafil efficacy and safety study (ASSESS-1): A double-blind, placebo-controlled, flexible-dose study of oral sildenafil in Malaysian,

Singaporean, and Filipino men with erectile dysfunction. The Assess-1 Study Group. **Urology 2000;56:635-640.**

5. Rendell MS, Rajfer J, Wicker PA, et al. Sildenafil for treatment of erectile dysfunction in men with diabetes: A randomized controlled trial. Sildenafil Diabetes Study Group. **JAMA 1999; 281:421-426.**
6. Fagelman E, Fagelman A, Shabsigh R. Efficacy, safety, and use of sildenafil in urologic practice. **Urology 2001;57:1141-1144.**
7. Hatzimouratidis K, Giuliano F, Moncada I, et al. EAU Guidelines on Erectile Dysfunction, Premature Ejaculation, Penile Curvature and Priapism 2018. European Association of Urology Guidelines. 2018 Edition. Arnhem, The Netherlands: European Association of Urology Guidelines Office; 2018.
8. Salhiyyah K, Forster R, Senanayake E, et al. Pentoxifylline for intermittent claudication. **Cochrane Database Syst Rev 2015; 9:CD005262.**
9. Ward A, Clissold SP. Pentoxifylline A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic efficacy. **Drugs 1987;34:50-97.**
10. Korenman SG, Viosca SP. Treatment of vasculogenic sexual dysfunction with pentoxifylline. **J Am Geriatr Soc 1993; 41:363-366.**
11. Peşkircioğlu L, Karabulut A, Deniz E, et al. The role of pentoxifylline in the treatment of erectile dysfunction due to borderline arterial insufficiency. **Br J Urol 1996;77:563-565.**
12. Ozdal OL, Ozden C, Gokkaya S, et al. The effect of sildenafil citrate and pentoxifylline combined treatment in the management of erectile dysfunction. **Int Urol Nephrol 2008; 40:133-136.**
13. Rosen RC, Cappelleri JC, Smith MD, et al. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. **Int J Impot Res 1999;11:319-326.**
14. Eardley I. Optimisation of PDE5 inhibitor therapy in men with erectile dysfunction: Converting "non-responders" into "responders". **Eur Urol 2006;50:31-33.**
15. Tamás V, Kempler P. Sexual dysfunction in diabetes. **Handb Clin Neurol 2014;126:223-232.**
16. Kumar S, Roat R, Agrawal S, et al. Combination therapy of tadalafil and pentoxifylline in severe erectile dysfunction; A prospective randomized trial. **Pol Przegl Chir 2015;87:377-383.**
17. Knoll LD, Benson RC Jr, Bilhartz DL, et al. A randomized crossover study using yohimbine and isoxsuprine versus pentoxifylline in the management of vasculogenic impotence. **J Urol 1996;155:144-146.**