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Investigation of a complex plant extract for mild to moderate erectile dysfunction in a randomized, double-blind, placebo-controlled, parallel-arm study

Andrea Ledda, Gianni Belcaro, Maria R. Cesarone, Mark Dugall and Frank Schönlau*

*Irvine Vascular Laboratories and Physiology, Department of Biomedical Sciences, Gabriele D'Annunzio University, Chieti-Pescara, Italy, and *Horphag Research UK Ltd, South Kensington, London, UK*

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Study Type – Therapy (RCT)
Level of Evidence 1b

OBJECTIVE

To assess the effects of a complex plant extract (Prelox®, a formulation of pine bark extract and L-arginine aspartate; Horphag Research UK Ltd, London, UK) on erectile dysfunction (ED) in men, as sexual desire typically persists in ageing men, while their erectile and endothelial function gradually declines.

PATIENTS AND METHODS

In this double-blind, placebo-controlled study we assessed the effects of Prelox in 124 patients (aged 30–50 years) with moderate ED over an investigational period of 6 months. The International Index Of Erectile Function (IIEF) was used to quantify changes in sexual function.

RESULTS

The erectile domain of the IIEF (questions 1–5 plus 15) improved with Prelox from a baseline mean (SD) score of 15.2 (6.6) to 25.2 (2.1) after 3 months and 27.1 (2.1) after 6 months of treatment. In the placebo group there was an increase from a baseline score of 15.1 (7.0) to 19.1 (3.0) and 19.0 (3.1) after 3 and 6 months, respectively. The effects with Prelox were statistically significant compared with placebo ($P < 0.05$). Mean (SD) total plasma testosterone levels increased significantly from 15.9 (2.3) to 18.9 (2.6) nmol/L ($P < 0.05$) after 6 months with Prelox, compared to an increase from 16.9 (2.4) to 17.3 (2.3) nmol/L in the placebo group.

CONCLUSION

This study shows that Prelox is effective for improving erectile function, and that this effect persists on continuous therapy for up to 6 months. Moreover, there is some evidence that erectile function continues to improve the longer the therapy is used.

KEYWORDS

erectile dysfunction, Prelox, L-arginine, erection problems, endothelial function

INTRODUCTION

Lifestyle plays an important role on the onset of erectile dysfunction (ED) and timely improvements such as healthier diet and exercise can significantly slow the progression to ED with increasing age. An intervention that helps to restore endothelial function would help to preserve the ability to spontaneously respond to sexual arousal. Prelox®, a patented complex formulation consisting of Pycnogenol® and L-arginine aspartate (Horphag Research UK Ltd, London, UK) has been shown in three clinical trials to restore healthy erectile quality in men presenting with moderate erectile problems [1,2].

Pycnogenol is a standardized extract of French maritime pine bark, consisting of 70 ± 5% procyanidins, oligomers of catechin and epicatechin, in accordance to US Pharmacopeia specifications. Further to the procyanidins Pycnogenol contains further flavonoid species including taxifolin, phenolic acids and monomeric catechin. Pycnogenol, the key component of Prelox, was shown in human pharmacological studies to act as catalyst on endothelial nitric oxide synthase for amplified synthesis of nitric oxide, the initial mediator for triggering an erection [3,4]. Furthermore, Pycnogenol alone has been found to improve erectile function in a pilot trial [5]. The combination with the enzyme's substrate L-arginine synergistically increases the synthesis of nitric oxide, the key component involved in vasodilatation for improved blood flow to engorge the penis [2].

All trials with Prelox have been carried out with relatively few patients for a short treatment duration of 4–6 weeks. Little is known about the sustained effects on the restoration of normal erectile function in men who continuously take Prelox over prolonged periods. We present our findings on the effects of Prelox over 6 months in 124 men with mild and moderate ED.

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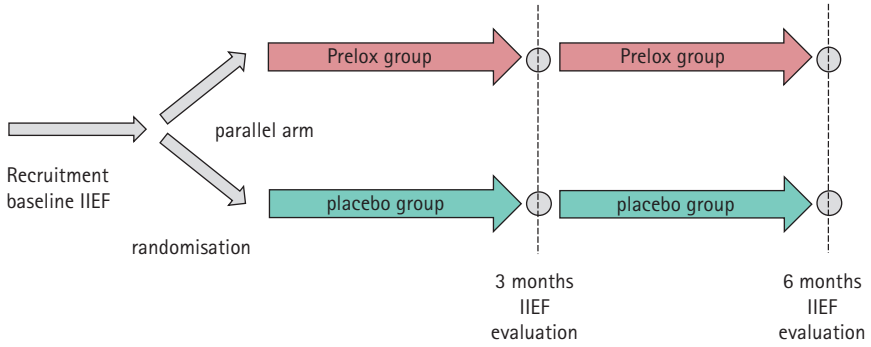
FIG. 1. A schematic illustration of the randomized, double-blind, placebo-controlled, parallel-arm study design.



PATIENTS AND METHODS

The primary index of erectile function was the erectile domain of the International Index of Erectile Function (IIEF) questionnaire [6]. The 'erectile domain' of the IIEF represents a subset of six questions of a total of 15 questions (questions 1–5 plus 15) related exclusively to scoring the erectile function, with values of 0–30.

A secondary outcome measure was the overall improvement of sexual well-being, as evaluated from patient's diaries. Further examinations comprised blood rheology and chemistry, blood pressure and testosterone levels.

The inclusion criteria for men to participate in the trial was age 30–50 years, a stable sexual partnership during the previous 6 months and mild to moderate ED, as judged by IIEF scores of ≥11–17. The men had a thorough physical examination during the first visit and after completing the trial to assess signs of hypogonadism, normal development of musculature, decrease in testicular volume, anatomical alterations of the penis, body fat distribution, voice, height, and vital signs, including blood pressure and heart rate. Men were interviewed for impairment of general performance, diminution of beard growth, decreased erection frequency, lessened sexual desire and fantasies, recent infections and inflammatory conditions, and harmful occupational or environmental health impacts.

The exclusion criteria comprised testicular maldescent, varicocele, orchitis, globozoospermia, disturbances of semen deposition (hypospadias), endocrine hypogonadism abnormality, psychiatric disorders, testicular tumours, infections, prostatitis or any other prostate problem, UTIs during the past 3 months, handicaps or anatomical problems affecting erections, surgery within the past 3 years, diabetes mellitus, severe hypertension (diastolic ≥90 mmHg; systolic ≥150 mmHg), renal failure, hepatic insufficiency, and clinical condition requiring medical treatment. Men suspected of using out-of-prescription drugs, alcohol or narcotics were also excluded.

The study was carried as a double-blind, placebo-controlled, parallel-arm trial, as illustrated in Fig. 1. Randomization was carried out by allocating patients to active or placebo groups by blocks. Block allocation sequences were created at random using randomly generated numbers from a computer program.

The standard regimen was two Prelox tablets taken between 07.00 and 09.00 hours, after breakfast, and another two tablets at 19.00–21.00 hours after dinner, with 200 mL water, respectively. Each Prelox tablet contained 20 mg Pycnogenol plus 700 mg L-arginine aspartate. Corresponding placebo tablets were matched for colour, size, shape and weight; tablets were oblong, blue and film-coated, 330 × 745 and 1100 mg (±5%). In the placebo tablets dicalcium phosphate replaced the active components. Tablets were manufactured by Manhattan Drug Company Inc, Hillside, NJ, USA. Investigators were not informed about the identity of tablets until after evaluation of the study results.

In all, 124 men completed the IIEF questionnaire at baseline and at monthly intervals over the 6-month treatment period. Fasting blood specimens were collected at baseline and after completing the 6-month period. Clinical chemistry was assessed using standard procedures for analysis. Haematology comprised haemoglobin and haematocrit values, and leukocyte, erythrocyte and thrombocyte counts. Standard assays were used for measuring glucose, total cholesterol, uric acid, albumin, aspartate amino-transferase, alanine amino-transferase and γ-glutamyl transpeptidase levels. Plasma total testosterone was quantified using the ACS 180 testosterone immunoassay (Bayer Health Care, Leverkusen, Germany).

Differences between groups were evaluated statistically using nonparametric (Mann–Whitney *U*-test) analyses of the variance, as the distribution of the IIEF score values cannot be considered parametric. $P < 0.05$ was considered to indicate significant differences, and values are given as the mean (SD).

RESULTS

Of the 124 men included, 111 completed the 6-month trial period (13 were lost to follow-up); 54 in the Prelox group and 57 in the control group completed the trial, respectively. The two groups did not differ significantly in age (Prelox 44.5 years, SD 4, controls 44.0, SD 4). Also blood chemistry, blood pressure and testosterone levels (which were within the normal range by inclusion criteria) were comparable in both groups at inclusion. The systolic blood pressures were not significantly different, at 138.9 (8.0) mmHg (Prelox) and 137.0 (6.8) mmHg (placebo). Patients were not taking antihypertensive medication before enrolment nor during this trial. Standard care was applied, with dietary suggestions for weight loss, decreased sodium intake and moderate exercise. Total cholesterol was borderline high with mean levels of 212 (12) mg/dL (Prelox) and 205 (18) mg/dL (placebo), for which none of the patients took medication. Fasting blood glucose was at healthy levels in all patients.

The erectile domain scores of the IIEF during the 6-month treatment period are shown in Fig. 2. The baseline erectile function score was comparable at baseline, at 15.2 (6.6) in the Prelox and 15.1 (7.0) in the control group. After 3 months of treatment the erectile function score increased significantly to 25.2

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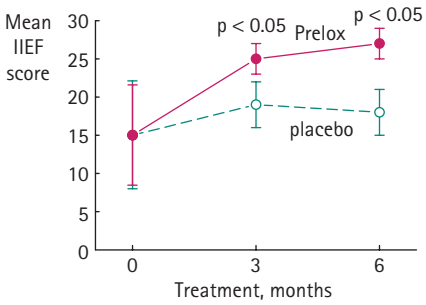
FIG. 2. The mean (SD) IIEF scores (erectile domain) of men taking Prelox or placebo (dotted line, open circles) over the treatment period. IIEF scores in the Prelox group were statistically significant vs placebo group scores.



(2.1) in the Prelox and 19.1 (3.0) in the placebo group ($P < 0.05$). After a further 3 months of treatment the IIEF score increased to 27.1 (2.1) in the Prelox and 19.0 (3.1) in the control group, which was statistically significant ($P < 0.05$).

Other domains of the questionnaire also improved to some extent; as shown in Table 1 the IIEF scores related to 'orgasmic function', 'sexual desire', 'intercourse satisfaction' and 'overall satisfaction' improved significantly in the Prelox group after 6 months of treatment, compared to corresponding scores in the placebo group ($P < 0.05$). Although there were changes from baseline in the placebo group these were not statistically significant.

Blood pressure decreased in the patients after completing the trial. The Prelox group showed a slight and insignificant decrease to 131.1 (7.3) mmHg systolic and 82.0 (4.3) mmHg diastolic blood pressure, respectively. The placebo group showed marginally decreased blood pressures of 135.0 (6.3) and 85.4 (6.1) mmHg, respectively. There were no effects of treatment on cholesterol and fasting blood glucose levels.

The total plasma testosterone level increased significantly in men taking Prelox, from the baseline of 15.9 (2.3) to 18.9 (2.6) nmol/L after 6 months, compared with the placebo group ($P < 0.05$), in which there was a limited increase from 16.9 (2.4) to 17.3 (2.3) nmol/L.

TABLE 1 The development of scores for additional domains of the IIEF, not related to erectile function. Prelox significantly improved the scores of all four additional domains after 6 months of treatment compared with scores in the placebo group ($P < 0.05$)

			Prelox		Control	
IIEF domain	Question	Score range	Baseline	6 months	Baseline	6 months
Orgasmic function	9, 10	0–10	5.1	9.0	5.2	6.5
Sexual desire	11, 12	2–10	5.0	9.1	5.0	6.0
Intercourse satisfaction	6, 7, 8	0–15	6.3	12.0	6.4	8.0
Overall satisfaction	13, 14	2–10	5.2	9.1	5.3	6.7

DISCUSSION

The results of the present study are in good agreement with those of other studies [1,2]. The present findings provide an insight into the durability of Prelox in a much larger group of men presenting with mild and moderate ED. The longest treatment duration with Prelox previously was 6 weeks [1].

A previous double-blind, placebo-controlled, cross-over investigation showed significant effects for improved erectile function after 1 month of treatment, which returned to baseline after a 1-month wash-out [7]. None of the previous studies offered information on whether improved erectile function would be retained with long-term use of Prelox. The primary measurement tool used in the present study was the IIEF and its individual domains, which is recognized to be the most reliable quantitative index of change in clinical trials, and is now standard in regulatory studies.

As anticipated from previous studies, the effect of Prelox was apparent at 3 months. Although not statistically significantly different, there was further improvement over the next 3 months. It can therefore be concluded that once established, the effect of Prelox might increase slightly over longer periods, and certainly there is no evidence of pharmacological tachyphylaxis. Encouragingly, at 6 months all domains of the IIEF were significantly improved beyond placebo. A study of the effect of Prelox over even longer periods would be of interest, although there is no reason to anticipate any diminution of the response.

In the present study we recruited exclusively a population of men with mild and moderate forms of ED, equivalent to a previous group [7]. In both studies patients were borderline hypertensive and Prelox slightly lowered the blood pressure. Other groups reported less pronounced improvements in erectile function with Prelox in men presenting with severe ED [1].

In a previous double-blind, placebo-controlled cross-over study [8,9] Prelox was associated with an increase in total plasma testosterone. Our study confirms this effect; there was a statistically significant increase in testosterone levels within the physiological range. As discussed by other authors, Prelox is unlikely to directly stimulate testosterone synthesis, but rather results from the phenomenon of increased intercourse activity enabled by enhanced erectile capability.

In conclusion, Prelox was again found to be effective in the treatment of mild to moderate ED. Importantly, the study shows that there appears to be no decline with habituation in the erectogenic action of Prelox, and there might indeed be a slight time-dependent augmentation. This study also shows that Prelox has an excellent benefit-risk profile, with few adverse events being reported.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

Frank Schönlau is an employee of Horphag Research; Gianni Belcaro is a study investigator for Horphag Research.

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Correspondence: Frank Schönlau, Horphag Research UK Ltd, 28 Old Brompton Road, Suite 393, South Kensington, London SW7 3SS, UK.
e-mail: frank@horphag.com

Abbreviations: **ED**, erectile dysfunction; **IIEF**, International Index of Erectile Function.

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