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A STUDY ON THE EVALUATION OF EFFICACY AND SAFETY OF A MULTIHERBAL PREPARATION (ANDROMET) IN ERECTILE DYSFUNCTION (ED): A RANDOMISED PLACEBO CONTROLLED TRIAL

Adhikari Anjan[1]*, Sen Krishna[2], Bhattacharya Kumkum[3], Biswas Sharmistha[4], Debnath Pratip Kumar[5]
[1]Department of Pharmacology, R G Kar Medical College, Kolkata, West Bengal, India
[2]Department of Medicine, R G Kar Medical College, Kolkata, West Bengal, India
[3]Department of Microbiology, R. G. Kar Medical College, Kolkata, West Bengal, India
[4]Department of Anatomy, N R S Medical College, Kolkata, West Bengal, India
[5]Consultant, National Research Institute of Ayurveda for Drug Development, Salt Lake, Kolkata, West Bengal, India

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***Corresponding author**
Email: dradhikarianjankolkata@gmail.com, aadhikari29@rediffmail.com

ABSTRACT
Erectile Dysfunction (ED) is a common problem with various aetiology. Recent advance discovered many drugs with specific mechanism of action. But till now there is no drug or medicine which is therapeutically successful. In Ayurveda, there was many formulations which can be tried on patients of ED. Present study is a double blind controlled randomised trial of efficacy and safety of a multiherbal preparation on ED. 35 patient of ED completed treatment with the multiherbal preparation (Andromet ™) compared with 15 patient of ED completed treatment with identical looking placebo as control. Results showed significant improvement in ED amongst the patients treated with multiherbal preparation (Andromet) in comparison with placebo treated group.
KEY WORDS: Andromet, Erectile Dysfunction, Clinical trial, Placebo

INTRODUCTION

Erectile dysfunction, sometimes, which also may imply to refer to "impotence," is the repeated inability to get or keep an erection for sexual intercourse[1,2]. The word "impotence" may also be used to describe other problems that interfere with sexual intercourse and reproduction, such as lack of sexual desire and problems with ejaculation or orgasm[1]. Roper[3] defines erectile dysfunction as the total inability to achieve erection, an inconsistent ability to do so, or a tendency to sustain only brief erections (premature ejaculation). Pamplona-Roger[4] defines impotence as the inability to finish sexual intercourse due to lack of penile erection. These variations make defining ED and estimating its incidence difficult.

The estimated range of men worldwide suffering from ED is from 15 million to 30 million[1]. According to the National Ambulatory Medical Care Survey (NAMCS), for every 1,000 men in the United States, 7.7 physician office visits were made for ED in 1985. By 1999, that rate had nearly tripled to 22.3. This is a clear indication that the prevalence of ED is alarming & it is spreading worldwide[3].

Erection of penis is a physiological event, it followed some sequence of events, ED can occur when any of these events is disrupted. This sequence includes nerve impulses in the brain, spinal column, and area around the penis, and response in muscles, fibrous tissues, veins, and arteries in and near the corpora cavernosa[1]. Thus, ED causes include, damage to nerves, arteries, smooth muscles, and fibrous tissues. These may be the result of diseases, such as diabetes, kidney disease, chronic alcoholism, multiple sclerosis, atherosclerosis, vascular disease, and neurologic diseases, studies showed that this account for about 70 percent of ED cases[1]. National Institute of Health (NIH) reported that between 35 and 50 percent of men with diabetes also suffered from ED.

Concomitant use of antihypertensive, antihistaminic, antidepressants, tranquilizers, appetite suppressants, and cimetidine (an peptic ulcer drug) can produce ED[1]. Nevertheless, psychological factors such as stress, anxiety, depression, low self-esteem, and fear of sexual failure cause 10 to 20 percent of ED cases[4]. Heavy smoking, which affects blood flow in veins and arteries, and hormonal abnormalities, such as lack of testosterone can aggravate ED[1].

In modern medication of ED, Viagra (Sildenafil) was very popular, when it was first launched. It acts by inhibiting cGMP-specific phosphodiesterase type 5, an enzyme that delays degradation of cGMP, which regulates blood flow in the penis. Since becoming available in 1998, sildenafil has been the prime treatment for erectile dysfunction. The most common adverse effects of sildenafil use included headache, flushing, dyspepsia, nasal congestion and impaired vision, including photophobia and blurred vision [5]. Due to its unwanted pharmacological actions it was also not so effective in patients of ED.Oral testosterone can reduce ED in some men with low levels of natural testosterone, but it is often ineffective and may cause liver damage[2]. Other drugs such as Yohimbine, Papaverine hydrochloride [used under careful medical supervision][2], Phentolamine, and Alprostadil (marketed as Caverject) dilates blood vessels[6]. However, this available medication for ED in men is very expensive, especially for most of the rural people in India and other developing countries. So, it is a timely conducted research work to evaluate the traditional medicine & medicinal plants in the treatment of ED.

World Health Organization estimated that in some Asian and African countries, 80% of the population depend on traditional medicine for primary health care [7]. This is an indication that herbal medicine is important in health care system in India. With these information and consideration this study was conducted to evaluate a multiherbal preparation in the ED in terms of efficacy and safety.

MATERIAL AND METHODS

This double blind placebo controlled study conducted in 50 non-alcoholic men, 30-70 years of age having a fixed sexual partner experiencing mild to moderate cases of sexual dysfunction for at least 6 months. Mild to moderate cases of sexual dysfunction, in this study means that, the person was not able to perform sexual intercourse satisfactorily with his fixed female partner at least once in three months. Symptoms of erectile dysfunction range from the inability to achieve or maintain an erection, premature ejaculation, the inability to ejaculate and below average libido levels.

The study was divided into two groups; at the commencement of the study both the groups comprises of 50 patients. But there was 15 drop out in the first group (group A) and 35 drop out in the second

group (group B). Group A had 35 patients and group B had 15 patients who completed the study. One group was treated with the test drug and the other group was treated with placebo for continuous 3 months period.

Group A was administered a polyherbal preparation (ANDROMET™), one tablet twice daily for three months. This polyherbal formulation contained *Chlorophytum borivilianum* 150 mg, *Anacyclus pyrethrum* 100 mg, *Tribulus terrestris* 100 mg, *Hygrophila auriculata* 50 mg, *Acacia arabica* 30 mg. The proportion of each ingredient was finalised after pilot studies to achieve maximum efficacy in ED.

Group B was administered identical looking and of identical weight placebo at a dose of one tablet twice daily. Patients were asked about erection size, strength and frequency of intercourse. Completed blood count and a blood biochemistry analysis including testosterone levels were done before and after treatment. This was for evaluation of safety of the tested multiherbal preparation.

Ethical clearance was taken from Institutional Ethical Committee and written informed consent was taken from each of them after clarification of the study. The patients were evaluated every two weeks in outdoor department in a hospital. Patients were evaluated with The International Index of Erectile Function (IIEF-5) Questionnaire (IIEF-5 questionnaire).Interventional period for test drug or the placebo was three months. Co-medications were continued as advised by the physician.

Statistical analysis was done in percentage, rate & ratios. The results were expressed as Mean±SE (Standard Error). Pair t-test was used for analysis of the test results and $P<0.05$ was considered significant.

RESULTS

Thirty five patients completed three months study period with the intervention of the multiherbal preparation (Andromet) and there was fifteen drop outs. In placebo treated group, 15 out of 50 patients completed the study and 35 patients dropped out at different stages of the study. Age distribution of both group A & Group B (Table 1 & 2) showed that in the test drug treated group (A), majority of the patients (34.3 %) were belonged to 60 to 69 years of age. Of these thirty five patients, 4 (11.4 %) was single with fixed female partner & 31(88.5 %) was married & five (14.3 %) patients had circumcision in childhood. In the group A, eight patients had co-morbid disease of diabetes mellitus & three had hypertension. Patients in the group B showed that maximum (40 %) patients were belonged to the age group of 60 to 69 years, Four (26.6 %) were single & eleven (73.3 %) were married, five (33.3 %) have circumcision. As per as co-morbidity was concerned in group B, four were suffering from diabetes mellitus and two were with hypothyroid. Patients were under medication for co-morbidity.

All the patients included in the study were evaluated biochemically. Blood report of the thirty five patient treated with the multiherbal preparation (Andromet) was shown in table 3. It showed that there was no significant change in the haematological parameters in the test drug treated group. There was no significant difference between the test drug treated group and the placebo treated group in the haematological parameters. Blood biochemistry was also done for each patient in the study both before and after the intervention. Table 4 & 5 showed that serum Cholesterol, Random Blood Sugar, Blood Urea Nitrogen (BUN), Serum Creatinine, Serum Glutamic-Oxaloacetic Transaminase (SGOT), another enzyme Serum Glutamate Pyruvate Transaminase (SGPT) & Serum Testosterone level in both group A & B, and there was no significant change in these results.

IIEF-5 questionnaire was evaluated in each patient at every two weeks. Significant improvements were observed with the IIEF-5 questionnaire and also in the sexual function record in the multiherbal treated (Andromet) group. There were significant improvements ($P<0.05$, $P<0.01$) in 3 of the 5 descriptive evaluations of the IIEF-5 questionnaire (Table 6 & 7). The sexual function record showed that 29 (80 %) patients showed fair to excellent improvement (Table 8 & 9) in the patients of test drug group.

DISCUSSION

This study was conducted in a district hospital to evaluate the efficacy of a multi herbal formulation (Andromet) in ED. Although many herbal and modern drugs are available for this disease, still there is a need for safe & more efficacious drug, which can ensure compliance. Andromet™ contains *Chlorophytum borivilianum* 150 mg, *Anacyclus pyrethrum* 100 mg, *Tribulus terrestris* 100 mg, *Hygrophila auriculata* 50 mg, *Acacia arabica* 30 mg.

Research already established the mechanism of action of saponins contained in *Chlorophytum borivilianum,* affect testosterone which has shown traces of stigmasterol as well as hecogenin. Both these components are ideal ingredients as anabolic in bodybuilding. Stigmasterol shares a similar structure with testosterone. It can be speculated that body receptors for testosterone may also interact with stigmasterol, to act nearly the same as testosterone. In similar fashion, hecogenin has an ability to convert to specific compounds that resemble testosterone structurally and yields the same results on the body.

An anabolic effect was observed in the test group compared to the control group, which was like the administration of testosterone suggesting a testosterone type action of the extracts[8]. The experiment suggested anabolic steroidal effect of *A. pyrethrum*. The enhancement of sexual activity has been directly correlated to the enhancement of sexual pleasure. Penile erection index is important for evaluating the effect of administration of the test drug on erectile function[9]. *Tribulus terrestris* a herb which restores and improves libido in men, improves and prolongs the duration of erection. It exerts a stimulating influence on spermatogenesis by increasing the number of spermatozoa and their mobility. It increases the level of testosterone also. It improves libido in women, exerts a slight stimulating ovulation effect, it has a favourable influence on vasomotor manifestation during natural and post-castration climacterium, as well as on subjective complains such as insomnia, general tenseness, irritability and apathy, etc[10].Fresh pods of *Acacia Arabica* tree are effective in sexual disorders like spermatorrhoea, frequent night discharges, loss of viscidity of the semen and premature ejaculation. Rasayana have been being used for the management of neurodegenerative diseases, as rejuvenators, immunomodulators, aphrodisiac and tonic[11].

In this study fifteen patients were dropped out at various stages of treatment in multiherbal treated (Andromet) group. Again thirty fife patients in the placebo treated groups were also dropped out after starting the drug (placebo). This was mainly due to some personal reasons, the patients informed about their inability to participate in the trial, but some patients were not satisfied with the drugs given to them. Only fifteen patients in placebo treated group completed their duration of therapy with placebo. None of the patients reported to have any adverse effects, both in the test drug treated group and also in the placebo treated group. Significant improvements were recorded with the IIEF-5 questionnaire and the sexual function record in the polyherbal (Andromet) treated group.

CONCLUSION

Search for better medicine for ED is a long term process. Research showed that, modern medicine available till now was not fully satisfactory to the patients of ED. Drugs of Ayurveda origin have a great potential for diseases like ED. Present study evaluated the safety & efficacy of a multiherbal preparation for ED. In this study, it was observed that this multiherbal formulation improved the overall performance in men with ED. Further study should be planned with a larger number of study populations, to establish the efficacy of the herbal drug. Research should be conducted at the

basic molecular level to explore the mechanism of action of this herbal combination in ED.

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Table1. Age distribution of patients in group A treated with the multi herbal preparation (Andromet) (n= 35).

Age (years)	Number & percentage of patients
30-39	5 (14.2 %)
40-49	8 (22.8 %)
50-59	10 (28.5 %)
60-69	12 (34.3 %)

Table 2. Age distribution of patients in group B treated with the placebo preparation (n= 15).

Age (years)	Number & percentage of patients
30-39	4 (26.6 %)
40-49	3 (20 %)
50-59	2 (13.3 %)
60-69	6 (40 %)

Table3. Haematological results of the patients of group A treated with multiherbal preparation (Andromet) (n=35).

Results of haemoglobin, haematocrit & differential count before and after the treatment	Hematology		Differential count (%)			
	Haemoglobin (g)	Haematocrit (%)	Neutrophil	Lymphocyte	Monocyte	Eosinophil
Pre-treatment	14±2.1	42±2.31	56±2.33	2.11±0.12	40.1±2.11	2.0±1.12
Post-treatment	13.2±1.21	41±2.11	54±3.12	2.89±0.23	39.67±2.67	3.0±1.34

Table 4. Blood biochemistry and testosterone level of multiherbal (Andromet) treated group (n=35).

Blood biochemistry parameters	Pre-treatment	Post-treatment
BUN (mg %)	11.23±2.12	10.34±2.3
Creatinine (mg %)	0.91±0.13	0.89±0.22
SGOT (U/L)	26.12±1.22	28.16±1.34
SGPT (U/L)	20.17±2.12	26.2±1.33
Cholesterol (mg %)	281.19±2.23	258.2±2.4
Sugar (mg %)	106.66±2.4	112.24±2.0
Testosterone (ng/mg)	2.16±0.22	3.18±0.37

Table 5. Blood biochemistry and testosterone level of placebo treated group (n=15).

	Pre-treatment	Post-treatment
BUN (mg %)	12.62±1.88	12.46±2.81
Creatinine (mg %)	0.88±0.16	0.76±0.19
SGOT (U/L)	28.12±1.62	29.66±1.77
SGPT (U/L)	22.0±2.32	24.2±1.63
Cholesterol (mg %)	256.22±1.65	260.2±3.83
Sugar (mg %)	108.62±2.4	117.24±2.34
Testosterone (ng/mg)	2.36±0.24	2.18±0.41

Table 6. IIEF-5 questionnaire based evaluation in the multiherbal preparation (Andromet) treated group (n=35).

Question	% Pre-treatment	% Post-treatment	Description
1	52.6	17.60*	No or not much enjoyment in sexual intercourse
2	76.5	31.45**	Low confidence for erection
3	49.12	14.80*	Almost never or never had erections with sexual stimulation hard enough for penetration
4	26.56	26.28	Almost never or never be able to maintain erection after penetration
5	81.16	21.50*	Difficult to maintain erection to completion of intercourse

*$P<0.05$, **$P<0.01$, compared with pre-treatment value.

Table 7. IIEF-5 questionnaire based evaluation in Placebo treated group (n=15).

Q	% Pre-treatment	% Post-treatment	Description
1	67.78	47.76	No or not much enjoyment in sexual intercourse
2	71.22	67.21	Low confidence for erection
3	55.16	51.12	Almost never or never had erections with sexual stimulation hard enough for penetration
4	31.23	27.12	Almost never or never be able to maintain erection after penetration
5	77.28	67.66	Difficult to maintain erection to completion of intercourse

Table 8. Sexual function record in multi herbal (Andromet) treated patients (n=35).

Score	Reaction	Evaluation	Number of patients (%)
0	-	No improvement	7 (15.5)
1	+	Fair improvement	8 (13.33)
2	++	Moderate improvement	4 (17.77)
3	+++	Good improvement	10 (35.55)
4	++++	Excellent improvement	6 (17.77)

Table 9. Sexual function record in Placebo treated patients (n=15).

Score	Reaction	Evaluation	Number of patients (%)
0	-	No improvement	12 (80)
1	+	Fair improvement	2 (13.33)
2	++	Moderate improvement	1 (6.66)
3	+++	Good improvement	NIL (0.00)
4	++++	Excellent improvement	NIL (0.00)

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