POLSKI
PRZEGLĄD CHIRURGICZNY
2015, 87, 8, 377–383

10.1515/pjs-2015-0075

DE GRUYTER
OPEN

ORIGINAL PAPERS

COMBINATION THERAPY OF TADALAFIL AND PENTOXIFYLLINE IN SEVERE ERECTILE DYSFUNCTION; A PROSPECTIVE RANDOMIZED TRIAL

SANTOSH KUMAR[1], RAJESH ROAT[2], SWATI AGRAWAL[1], KUMAR JAYANT[3], RAVIMOHAN S. MAVUDURU[3], SHRAWAN KUMAR[3]

Postgraduate Institute of Medical Education and Research, Chandigarh, India[1]
Department of General Surgery, PGIMER, Chandigarh, India[2]
Department of Urology, PIGMER, Chandigarh, India[3]

The aim of the study was to assess efficacy of Tadalafil alone versus Tadalafil plus Pentoxifylline in the treatment of erectile dysfunction by using self administered IIEF-5 questionnaire.
Material and methods. Two hundred and thirty seven patients presenting with ED at andrology OPD were evaluated for ED by a self administered IIEF (International Index of Erectile Function) questionnaire. Patients were systematically randomized by computer generated random table into two groups groups namely, group A: Tadalafil only group, group B: combination of Tadalafil + Pentoxifylline. All the patients were re-assessed by IIEF-5 questionnaire after 8 weeks of medical therapy. Statistical analysis was performed using student's unpaired t-test, paired t-test, chi square test. p-value < 0.05 was considered statistically significant.
Results. Two hundred and thirty seven patients were included in the present study, in group A: 92 patients (78.6%) showed improvement in their IIEF score after 8 weeks of tadalafil treatment. While in group B, overall 104 patients(86.6%) showed improvement after combination of Tadalafil and Pentoxifylline. There was a statistically significant difference of percentage change in IIEF score was seen in group B (group A 90.7±15.2%, group B 95.6±13.4%; p value – 0.014). We found this difference even more statistically significant in patients with severe ED (group A 72.7±47.2%, group B 132.3±54.3%; p value – 0.000). There was no significant difference in between the two groups with regards to occurrence of side effects.
Conclusions. Both tadalafil and combination of Tadalafil + Pentoxifylline improve erectile function in patients of ED. Patients with severe ED showed much significant improvement in erectile function with combination therapy.
Key words: erectile dysfunction, PDE5 inhibitors, Tadalafil, Pentoxyfilline

Erectile dysfunction (ED) is a common emerging problem all over the world. It more commonly affects the older age group as compared to the younger. Over 150 million men all over the world are affected, with a prevalence of 52% in men aged 40 to 70 years. The diagnosis and treatment of erectile dysfunction provides opportunities to enhance patient's health and well-being (1). It is frequently associated with several comorbid conditions, like cardiovascular disease, diabetes mellitus, hypertension and lower urinary tract symptoms. These conditions often have major consequences on the quality of life of the patients. The degree of ED varies directly with the number of arterial risk factors, including hypertension, hyperlipidemia, type 2 diabetes mellitus and smoking (2). Many treatment modalities are available for the treatment of ED. In erectile dysfunction and pulmonary hypertension, phosphodiesterase inhibitors are used for many years. In the present study, we aim to evaluate the

efficacy of tadalafil alone with the combination of Tadalafil and Pentoxifylline in the treatment of erectile dysfunction (3).

MATERIAL AND METHODS

All the patients presenting with ED at our andrology OPD of from 1st July 2011 to 31th December 2012 were evaluated for ED by a self administered questionnaire IIEF.

Sample size was calculated a priori with the alpha level set at 0.05, an anticipated effect size (Cohen's *d*) of 0.5 and a desired statistical power level of 0.90. The required sample size per group was 86. Unpaired and paired student t test and chi-square test were used for the analysis of the variables and categorical data. Differences were considered significant at a *p* value less than 0.05.

Those patients with ED who satisfied the inclusion criteria and gave informed consent were systematically randomized by a computer generated random table into two groups namely: group A: Tadalafil only (10 mg OD) & group B: combination of Tadalafil (10 mg OD) + Pentoxifylline (1200 mg in three divided doses) for 8 weeks. All patients were evaluated by physical examination, hormonal assay, hematological and biochemical investigations including fasting blood sugar and lipid profile.

ED was assessed by IIEF-5 self administered questionnaire. All the patients were reassessed by IIEF-5 questionnaire after 8 weeks of medical therapy. Any side effects like nausea and vomiting, dyspepsia, headache, myalgia, backache, flushing, leg pains etc. After start of the treatment, either self reported by the patient or by direct enquiry were recorded as occurrence of side effects. Statistical analysis was performed using student's unpaired t-test, paired t-test, chi square test. p-value < 0.05 was considered statistically significant. Data was fed into a Microsoft Excel worksheet and was analyzed by using the SPSS ver. 17 (SPSS Inc., Chicago, USA).

RESULTS

Two hundred and fifty three patients were included in the present study (fig. 1). Amongst them, 11 patients had history of recent intake of PDE-5 inhibitors and other 5 denied to participate, so they were excluded from the study. Of the remaining 237, patients were randomly

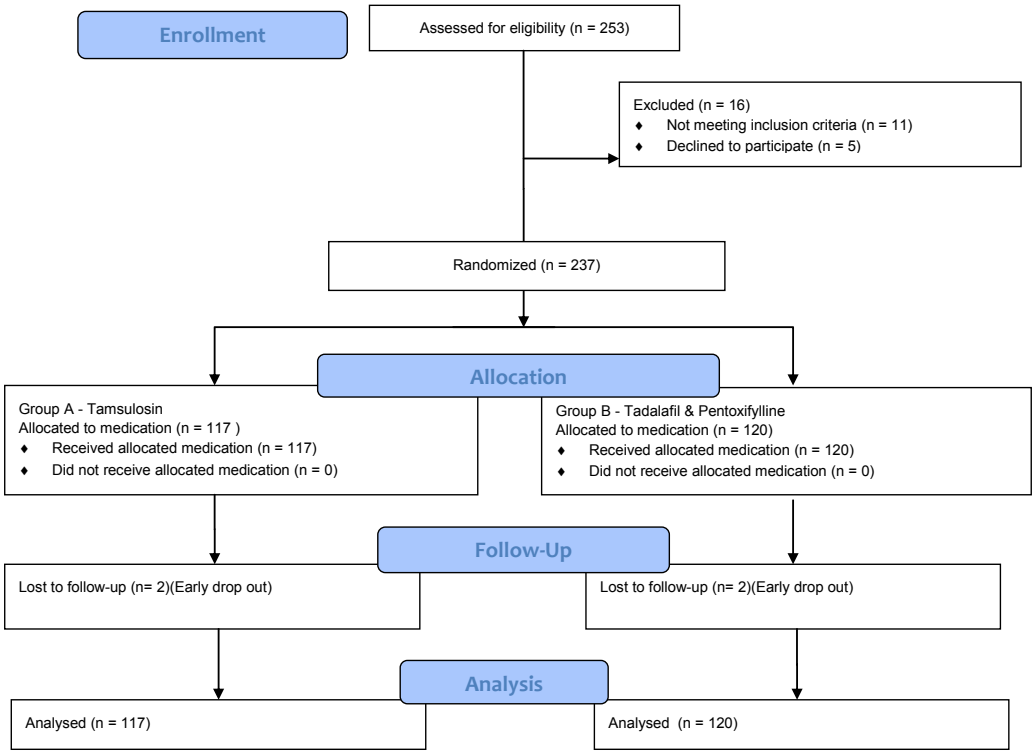

Fig. 1. Flow chart showing the study design

divided into the two groups. In the group A (Tadalafil 10 mg OD for 8 weeks) there were 117 patients and in the group B (Pentoxifylline 400 mg TDS plus Tadalafil 10 mg OD for 8 weeks) there were 120 patients. Baseline patient demographics, age (40-55 yrs) and clinical characteristics were similar in both the groups. Eighteen patients had type 2 diabetes mellitus (7.4%), 33 patients were hypertensive (14.4%), 43 patients were smokers (19.4%) and 67 had history of alcohol use (31.8%) (tab. 1). All of these variates are equally present in both groups. The pre-therapy IIEF scores were low, suggestive of erectile dysfunction in both the groups (p=0.04). Furthermore, on subgroup analysis there was no significant difference in the erectile dysfunction between the two groups. ED in both the groups was categorized based on IIEF scores into mild (17-21), mild to moderate (12-16), moderate (8-11) and severe (5-7).

Patients in both the groups showed significant improvement in their IIEF scores after eight weeks of treatment With Tadalafil in group A, the improvement in IIEF scores was statistically significant in mild to moderate and moderate subgroup of patients but not significant in the severe subgroup. The IIEF scores of patients in group B improved significantly after treatment, in all the subgroups (tab. 2, 3).

Table 1. Demographic data

	Group A (n=117) (mean±SD)	Group B (n=120) (mean±SD)	p value
Age(mean ± SD)	46,73 ± 6,7	47 ± 7,01	0,637
Testosterone	41,19 ± 98,92	31,06 ± 88,69	0,969
Sugar profile			
• fasting sugars	92,88 ± 24,56	92,13 ± 10,18	0,598
• postprandial sugars	127,86 ± 40,29	116 ± 22,58	0,086
Lipid profile			
• CH	203,42 ± 39,60	198,68 ± 41,03	0,619
• TG	157,36 ± 66,62	151,36 ± 66,62	0,706
• HDL	47,81 ± 23,99	46,31 ± 10,42	0,722
• VLDL	32,78 ± 15,05	33,04 ± 14,52	0,940
• LDL	116,64 ± 42,66	115,69 ± 34,11	0,916
Serum creatinine	0,718 ± 0,18	0,679 ± 0,18	0,231
Smoking	18 (18,2%)	21 (20,5%)	0,244
Alcohol	33 (33,6%)	31 (30,3%)	0,711
Comorbidity			
• DM	7 (7,1%)	8 (8,0%)	0,586
• HTN	10 (10%)	9 (8,8%)	1,000

Group A: Tadalafil
Group B: combination of Tadalafil + Pentoxifylline
a: statistical significance was analyzed by chi-square test
b: statistical significance was analyzed by unpaired Student's t-test

Table 2. Mean IIEF Score before and after Tadalafil treatment in group A and group B

ED degree	Before treatment (mean±SD)	After treatment (mean±SD)	p value
Group A			
Mild to moderate (29)	13,88 ± 1,36	21,08 ± 1,83	< 0,001
Moderate(54)	9,66 ± 1,18	19,50 ± 3,76	< 0,001
Sever e (16)	6,60 ± 0,89	11,40 ± 6,22	0,092
Group A			
Mild to moderate (27)	13,33 ± 1,74	22,27 ± 2,45	< 0,001
Moderate (54)	9,70 ± 1,14	21,30 ± 3,80	0
Severe (21)	6,30 ± 0,90	14,64 ± 6,61	0

Group A: Tadalafil
Group B: combination of Tadalafil + Pentoxifylline
a: Statistical significance was analyzed by paired Student's t-test

Table 3. Mean IIEF Score before and after Tadalafil treatment in group A and group B (comparative subgroup analysis)

ED degree	Group A (Tadalafil)			Group B (Tadalafil + Pentoxifylline)		
	pretherapy IIEF(mean±SD)	pretherapy IIEF(mean±SD)	% change in IIEF	pretherapy IIEF(mean±SD)	pretherapy IIEF(mean±SD)	% change in IIEF
Overall	9,90 ± 2,75	18,88 ± 4,74	90,70 ± 15,2	10,10 ± 2,81	19,78 ± 4,86	95,6 ± 13,4
Mild-moderate	13,88 ± 1,36	21,08 ± 1,83	54,08 ± 11,5	13,63 ± 1,74	22,27 ± 2,45	63,38 ± 24
Moderate	9,66 ± 1,18	19,50 ± 3,76	101,8 ± 36,80	9,70 ± 1,14	21,30 ± 3,80	119,5 ± 38,5
Severe	6,60 ± 0,89	11,40 ± 2,60	72,70 ± 47,2	6,3 ± 0,90	14,64 ± 6,61	132,30 ± 54,3

Group A: Tadalafil
Group B: combination of Tadalafil + Pentoxifylline
a: Statistical significance was analyzed by unpaired *Student's* t-test

In group A 92 patients (78.6%) showed improvement in their IIEF score after 8 weeks of tadalafil treatment. Of these, 33 patients (27.2%) improved to normal, 49 patients (41.8%) improved to mild ED and 10 patients (8.5%) to mild-moderate. In group B, overall 104 patients (86.6%) showed improvements after combination of Tadalafil and Pentoxifylline. Out of these 38 patients (31.6%) improved to normal and 54 patients (45%) showed improvement up to mild ED, 12 patients (10%) showed improvement up to mild- moderate group. Forty one patients (17.2%) did not respond to any treatment (twenty five in group B and sixteen in group A).

For analysis the percentage change in IIEF scores were calculated for each patient using the following formula.

$$\% \text{ change in IIEF} = \frac{\text{post therapy IIEF} - \text{pre therapy IIEF}}{\text{pretherapy IIEF}} \times 100$$

There was a statistically significant difference 18.5 between the percentage change in between the two groups (group A 78.2±10.2%, group B 96.08±16.4%; p value – 0.000). Similarly the percentage change in IIEF scores after treatment in both groups based on post therapy sub groups comparisons were statistically comparable. Also subgroup comparison in both the groups have showed better outcome with Tadalafil & Pentoxifylline group while best results are seen with the comparison of severe ED subgroup (group A 72.7±47.2%, group B 132.3±54.3%; p value – 0.000) (tab. 3, 4).

Overall side effects as experienced by the patients in both groups are tolerable and there was two incidences of lost to follow up in each group. There was no major side effects noted by any patient in either group and all of them had successfully completed the treatment course. Few minor adverse effects were noticed in each group. As in group A headache was present in 9 patients, back pain in 4 and nasal stuffiness was noted in 2 while in group B, 11 patients had headache, back pain in 3 and nasal stuffiness was present in 2. There was no significant difference in between the two groups with regards to occurrence of side effects (tab. 5).

DISCUSSION

Penile erection is a complex neurovascular phenomenon of coordinated hemodynamic events involving the interaction of nerves, neurotransmitters, striated and smooth muscle and tunica albuginea. ED can result from any alteration in one of these components. It has been defined as a major health problem affecting 52% of men between the ages of 40 and 70 years (4). Various treatment options presently used for ED include oral therapy, psychogenic counselling, vacuum device, vasoactive drug injections, transurethral drug therapy, vascular surgery and penile implants. Patients with severe organic erectile dysfunction have demonstrated a strong preference for oral agents even if they have lower response rates than for intracavernosal injections or penile implants (5, 6, 7). In ED and pulmonary hypertension, PDE5 inhibitors are used since many years. A PDE5 inhibitor is a drug used to block the degradative action of PDE5 on cyclic GMP in the smooth muscle cells lining the blood vessels supplying the corpus cavernosum of the penis. These drugs were the first effective oral treatment available for this condition and are considered as first line treat-

Table 4. Intergroup comparison based on various categories of ED subgroups

IIEF5 pre therapy	Group	Patients	Mean IIEF (% change) ±SD	p value
Overall	A	117	90,70 ± 15,20	0,014
	B	120	95,6 ± 13,40	
Mild to moderate	A	29	54,08 ± 11,52	0,027
	B	27	63,38 ± 24	
Moderate	A	58	101,80 ± 36,80	0,012
	B	58	119,50 ± 38,50	
Severe	A	30	72,70 ± 47,20	0
	B	35	132,30±54,30	

Group A: Tadalafil
Group B: combination of Tadalafil + Pentoxifylline
a: Statistical significance was analyzed by unpaired Student's t-test

Table 5. Treatment related side effects between the two groups

Adverse effect	Group A	Group B	p value
Headache	9	11	0,34
Back-Pain	4	3	0,89
Nasal stuffiness	2	1	0,78

Group A: Tadalafil
Group B: combination of Tadalafil + Pentoxifylline
a: Statistical significance was analyzed by unpaired Student's t-test

ment of ED after a detailed analysis by history, examination and invasive diagnostic modalities (8, 9,10). Although sildenafil, vardenafil, and tadalafil all work by inhibiting PDE5, Tadalafil's pharmacologic distinction is its longer half-life (17.50 hours) – compared to sildenafil (4-5 hours) and vardenafil (4-5 hours) (11-15). Furthermore, the longer half-life is the basis for Tadalafil's daily therapeutic use in relieving pulmonary arterial hypertension.

Recent observations suggest that daily dose of short term Tadalafil improves ED and endothelial dysfunction (16, 17, 18). Pentoxifylline is a xanthine derivative drug classified as a hemo-rheologic agent that affects blood viscosity. It improves the flow properties of blood by decreasing its viscosity. In patients with chronic peripheral arterial disease this agent increases blood flow to the affected microcirculation and enhances tissue oxygenation. The effects of Pentoxifylline and its clinical use in cerebral and peripheral arterial diseases suggested that it might be effective in improving penile blood flow and potency in men with mild to moderate vasculogenic impotence. It was reported that Pentoxifylline therapy regularly increased the penile brachial pressure index in impotent men, in comparison with a placebo (19, 20, 21). Based on these observations we had undertaken this pilot study wherein we compared the effect of Tadalafil and combination of Tadalafil and Pentoxifylline in a randomized prospective manner.

We studied two hundred and thirty seven patients in the present study. The mean age of the patients was 46.15 ± 9.39 years (p value=0.637). The demographic profile of both the groups was comparable, and none of the known risk factors of ED were different in between the groups. We excluded all the patients with possible psychological, endocrinological causes of ED before any PDE5 inhibitors or combination was administered. ED improved in both the groups after 8 weeks of treatment but analysis of change in percentage of IIEF score had showed better result in group B (group A-91.7±15.2; group B-96.4±13.4, p=0.014).

We found a similar finding in comparison of subgroups analysis in both group while best results were seen with patients in severe ED subgroup treated with Tadalafil and Pentoxifylline (p=0.000).

This reiterates the fact that Tadalafil and combination are effective in treatment of ED but in severe cases of ED the combination of the drugs may show a possible better improvement (22). This is in accordance of a study by Ozdem et al. wherein he studied 68 patients

of vasculogenic ED and compared the efficacy of sildenafil with combination of Sildenafil and Pentoxifylline. He found that the IIEF scores improved by 5.62± 2.08 in the Sildenafil only group whereas increase in the IIEF score was 9.51±3.77 in the combination therapy group. There was a statistically significant increase in the combination group when compared to the Sildenafil only group ($p<0.001$) (23). In another small study Peskircioglu et al. showed significant increase in PSV (Peak systolic Velocity) at the end of the Pentoxifylline treatment. The mean change in PSV achieved by Pentoxifylline treatment (6.25 cm/s) was significantly higher than that achieved by the placebo (0.38 cm/s). Seven patients had a positive response (successful coitus achieved after treatment with Pentoxifylline) (24).

Our study was the first study of its kind, here we compared tadalafil with combination of Tadalafil and Pentoxifylline in the management of ED, where the medications are administered after the initial screening of ED and before any invasive diagnostic procedures.

On inter group comparisons it was observed that the improvements in IIEF scores as assessed by percentage change in IIEF scores were statistically significant between the two groups (p value=0.016). This was more seen in severe ED subgroups patients who showed better outcome with combination drugs. The group B patients had statistically significant % IIEF improvement in comparison to group A. (group A-72.7±47.2; group B-132.3±54.3, p=0.000)

CONCLUSIONS

Hence we conclude that combination of Tadalafil + Pentoxifylline showed significant improvement in IIEF scores in patients of ED. Further we also want to emphasize that this improvement was more seen in patients with severe ED who received combination of Tadalafil 10 mg OD + Pentoxifylline 1200 mg in three divided doses.

REFERENCES

1. *Lizza EF, Rosen RC:* Definition and classification of erectile dysfunction: report of the Nomenclature Committee of the International Society of Impotence Research. *Int J Impot Res* 1999; 11: 141-43.
2. *Aytaç IA, McKinlay JB, Krane RJ:* The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. BJU Int 1999; 84: 50-56.
3. *Feldman HA. Goldstein I, Hatzichristou DG* et al.: Impotence and its medical and psychosocial correlates: results of the Massachusetts male aging study. *J Urol* 1994; 151: 54-61.
4. *Daugan, A; Grondin P, Ruault C* et al.: The discovery of tadalafil: a novel and highly selective PDE5 inhibitor. 1: 5,6,11,11a-tetrahydro-1H-imidazo(1',5': 1,6)pyrido(3,4-b)indole-1,3(2H)-dione analogues. *J Med Chemistry* 2003; 46(21): 4525-2.
5. *Jayant, K, Agrawal, R Agrawa, S:* Tamsulosin versus tamsulosin plus tadalafil as medical expulsive therapy for lower ureteric stones: A randomized controlled trial. *Int J Urol* 2014; doi: 10.1111/iju.12496.
6. *Ward A, Clissold SP:* Pentoxifylline. A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic efficacy. *Drugs* 1987; 34: 50-97.
7. *Saenz de Tejada I, Goldstein I, Azadzoi K* at al.: Impaired neurogenic and endothelium-mediated relaxation of penile smooth muscle from diabetic men with impotence. *N Engl J Med* 1989; 320: 1025-30.
8. *Carrier S, Nagaraju P, Morgan DM* at al.: Age decreases nitric oxide synthase -containing nerve fibres in the rat penis. *J Urol* 1997; 157: 1088-92.
9. *Burchardt M, Burchardt T, Baer L* et al.Hypertension is associated with dysfunction. *J Urol* 2000; 164: 1188-91.
10. *Sadovsky R, Miller T, Moskowitz M, Hackett G:* Three-year update of sildenafil citrate (Viagra) efficacy and safety. *Int J Clin Pract* 2001; 55: 115-28.
11. *Chen KK, Hsieh JT, Huang ST* at al.: ASSESS-3: a randomised, double-blind, flexible-dose clinical trial of the efficacy and safety of oral sildenafil in the treatment of men with erectile dysfunction in Taiwan. *Int J Impot Res* 2001; 13: 221-29.
12. *Knapp PM, Seftel AD, Wilson SK* at al.: The efficacy and safety of tadalafil in United States and Puerto Rican men with erectile dysfunction. *J Urol* 2004; 172: 652-57.
13. *Nagao K, Ishii N, Kamidono S, Osada T:* Safety and efficacy of vardenafil in patients with erectile dysfunction: result of a bridging study in Japan. *Int J Urol* 2004; 11: 515-24.
14. *Boolell M, Gepi-Attee S, Gingell JC* at al.: Sildenafil,a novel effective oral therapy for male erectile dysfunction. *Br J Urol* 1996; 78: 257-61.

15. *Yaman O, Tokath Z, Inal T, Anafarta K:* Effect of sildenafil on nocturnal erections of potent men. *Int J Impot Res* 2003; 15: 117-21.
16. *Rosen RC, Padma-Nathan H, Shabsigh R* at al.: Determining the earliest time within 30minutes to erectogenic effect after tadalafil 10 and 20 mg: multicenter, randomized, double-blind, placebo controlled, at-home study. *J Sex Med* 2004; 1: 193-200.
17. *Santosh K, Kumar J, Agrawal S, Singh SK:* Comparative efficacy of tamsulosin versus tadalafil in combination with prednisolone for the medical expulsive therapy of lower ureteric stone: A randomized trial. *Korean J Urol* 2014 Mar; 55(3): 196-200.
18. *Chris McMahon:* Efficacy and Safety of Daily Tadalafil in Men with Erectile Dysfunction Previously Unresponsive to On-demand Tadalafil *J Sex Med* 2004; 1: 292-300.
19. *Brock GB, McMahon CG, Chen KK* et al.: Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. *J Urol* 2002; 168: 1332-36.
20. *Hellstrom WJ, Gittelman M, Karlin G* et al.: Vardenafil for treatment of menwith erectile dysfunction: efficacy and safety in a randomized, double-blind, placebo-controlled trial. *J Androl* 2002; 23: 763-71.
21. *Knoll LD, Benson RC Jr, Bilhartz DL* at al.: A randomized crossover study using yohimbine and isoxsuprine versus pentoxifylline in the management of vasculogenic impotence. *J Urol* 1996; 155: 144-14.
22. *Kruuse C, Jacobsen TB, Thomsen LL* at al.: Effects of the non- selective phosphodiesterase inhibitor pentoxifylline on regional cerebral blood flow and large arteries in healthy subjects. *Eur J Neurol* 2000; 7: 247-53.
23. *Ozdem Levent Ozdal, Cuneyt Ozden, Serkan Gokkaya* et al.: The effect of sildenafil citrate and pentoxifylline combined treatment in the management of erectile dysfunction, *Int Urol Nephrol* 2008; 40: 133-36.
24. *Peskircioglu L, Karabulut A, Deniz* E at al.: The role of pentoxifylline in the treatment of erectile dysfunction due to borderline arterial insufficiency. *Br J Urol* 1996; 77: 563-65.

Received: 20.05.2015 r.
Adress correspondence: Podyplomowy Instytut Edukacji Medycznej i Badań, Chandigarh, Indie
e-mail: santoshsp1967jaimatadi@yahoo.co.in