

A Prospective Randomized Comparative Study to Evaluate the Effect of Once Daily Dose of Tadalafil (5 mg) vs. On-Demand Tadalafil (10 mg) on International Index for Erectile Function (IIEF) Score

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ABSTRACT

BACKGROUND

Erectile dysfunction is a common condition affecting middle and old age men throughout the world. Tadalafil is preferred by many urologists as well as patients because of its long half-life. Tadalafil on demand was compared with daily dosing in many studies. We wanted to conduct the study in south India at a tertiary care medical center to study the effect of tadalafil daily (5 mg) vs. on demand (10 mg) and check its efficacy with the IIEF scoring system.

METHODS

Patients were randomised into two groups using simple randomization chit box method. Allocation concealments was done by sealed enveloped method. Before starting treatment IIEF scoring was done for both groups. Group A was given once-daily 5 mg tadalafil. The group B was given 10 mg tadalafil before sexual activity. All patients under either of the two medication regimens for a period of 12 wks. and assessment done at 4 wks. and 12 wks. interval. Both the patient and the examiner was blinded to the randomisation of the subjects. Scoring scale is 1 to 30 which is divided into five groups of severe, moderate, mild to moderate, mild, and no dysfunction for score of 0 - 10, 11 - 16, 17 - 21, 22 - 25, and 26 - 30 respectively.

RESULTS

Tadalafil 5 mg OD has statistically significant better result when compared with IIEF score after 4 wks. with percentage improvement of 21.12 % when compared to baseline, with a P value of < 0.0001. In group II tadalafil 10 mg on demand shows statistically significant results when IIEF score baseline was compared with that after 4 wks. When group I compared with group II for mean difference of score after 4 wks. group I shows statistically significant improvement with P value 0.017 (< 0.05). When compared with score after 16 wks. with baseline both group I and II shows statistically significant improvement in IIEF score. But group I which shows mean difference in score of 5.40 (42.05 % improvement from baseline) is a statistically significant difference (p value - 0.0001) when compared to group II which shows mean difference of score at 16 wks. as 2.73 (20.71 % improvement from baseline).

CONCLUSIONS

Tadalafil 5 mg daily provides significant increase in IIEF score as compared to on demand 10 mg tadalafil. We need longer duration of study the side effects in each group.

KEYWORDS

Tadalafil, IIEF, Once a Day, On Demand, Erectile Dysfunction

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BACKGROUND

Throughout the world, erectile dysfunction is a common condition affecting men of middle and old age group.¹ Its incidence is increasing over the world during the last few decades² which could be attributed to many reasons. But one significant reason being the availability of PDE5 inhibitors, now people with ED are coming more frequently for treatment than in the past.³

Erectile dysfunction has been defined as "The inability to achieve / maintain penile erection which leads to unsatisfactory sexual intercourse".¹ ED incidence is 6 % in 20 - 29 yrs. age group, and 50 - 70 % in 40 to 79 yrs.² India is fastest growing population in the world and majority of them are males, due to high incidence of lifestyle related diseases such as obesity, hypertension, DM (Diabetes Mellitus) it is projected that incidence of ED might increase to 320 million by 2025.³ Its incidence is increasing over the world during the last few decades, which could be attributed to many reasons. But one significant reason being the availability of PDE5 inhibitors, now people with ED are coming more frequently for treatment than in the past.³

Erection is a very complex process which needs fine interaction of vascular, neurogenic, hormonal, and penile smooth muscle cells.⁴ Aetiology is variable ranging from psychological or physiological factors including lifestyle, vascular cause, testosterone deficiency, DM, and aging.⁵ Erectile dysfunction isn't just sexual disease, it affect quality of life and is associated with many psychosocial aspect of life pushing men to conditions such as depression, low self-esteem, anxiety about performing sexual activity and suicide.⁶

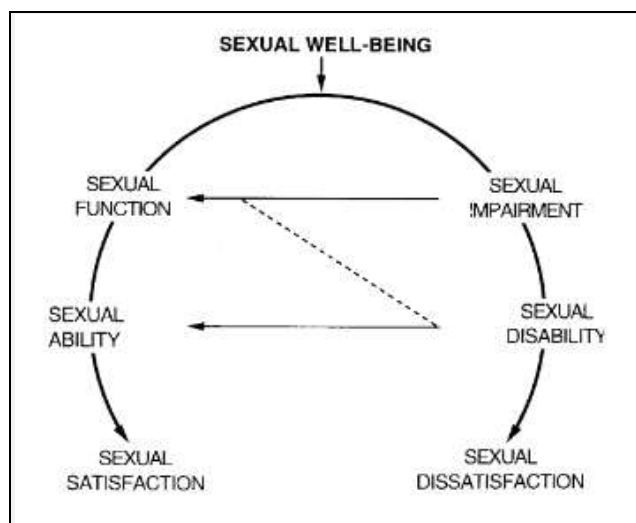


Figure 1. A Conceptual Model for the Analysis of Sexual Problems and Their Potential Effect on Sexual Satisfaction⁶

Various scoring and grading systems are used to measure Erectile Function (EF). The most commonly preferred method of ED is the "International Index for Erectile Function and Erectile Function domain (IIEF-EF)".⁶ The International Index of Erectile Function score is used all over the world by most treating physicians, it is easy to follow by patient and a self-reporting tool which has various aspect of sexual function making it multidimensional it's also

a grading tool for measurement of male sexual function. It is used as a primary endpoint for many clinical trials on erectile dysfunction and helps to diagnose the severity of ED. IIEF was developed along with sildenafil trials and had shown great ease in assessing the sexual function and determining severity of disease and since then it is considered as "Gold Standard" for assessment of ED. It has been translated in thirty-two different languages and used as a primary endpoint in more than 50 clinical trials on ED.⁷ Total score is 30 points, which is divided into mild, moderate and severe based on score to denote severity of ED. This scoring has been used in various studies as to assess ED.⁸ The advantage of this questionnaire is that it is easy to understand by patient and can be scored by patient himself that makes it great tool in various research and clinical trials, and it has the requisite sensitivity and specificity required to diagnose and detect any treatment-related changes in patients with ED.

No ED	25-30
Mild	19-24
Mild to Moderate	13-18
Moderate	7-12
Severe	0-6

Table 1. There are Five Classes of IIEF Score

The questionnaire is composed of 15 different items over the various aspect of male sexual dysfunction such as ejaculatory problem, problem related to intercourse, erectile dysfunction, disorder of orgasm, overall satisfaction, and there is also an abbreviated format of the five questions which can also be used as well: the Sexual Health Inventory for Men (SHIM). The IIEF is widely used and, as shown below, in combination with objective measures, used for the evaluation of the adequacy of sexual functioning.⁹ Phosphodiesterase type 5 (PDE5) inhibitors are proved to be effective in multiple studies done for ED. Tadalafil is preferred by many urologists as well as patients because of its long half-life. Tadalafil on demand was compared with daily dosing in several studies. Various dose combinations and dosage schedule have been studied such as 5 mg, 10 mg, 20 mg. Many tests conducting the efficacy of tadalafil on-demand vs. daily dosing have been done in Western and East Asian country population

In India, ED is still considered taboo, and with awareness and availability of treatment options, many patients with ED are seeking consultation for treatment. Number of people using ED medical therapy is very low and people continuing therapy are lower than expected.¹⁰ There is a clear-cut deficiency in studies and data on drug utilization and its compliance among Indian men. As the incidence of ED is rising and we will reach sky high in the coming decade, it's utmost important to have a clear consensus on drug dosages, the duration for management of erectile dysfunction.

We conducted the study in South India at a tertiary care medical centre to see tadalafil (5 mg) once a day dosage schedule compared to tadalafil 10 mg on demand dosage and we are using IIEF scoring method to assess this. These dosages have already been studied in independent studies.

METHODS

This is a randomized double-blind study that was conducted from 2018 - 2020 at the Urology Department of Vijayanagar Institute of Medical Sciences, Bellary. The patients having a convincing history of ED as per the definition of ED by NIH (National Institutes of Health) were included in the study. Detailed history and demographic details were taken from all patients who are included in study.

Inclusion Criteria

- All patients with the diagnosis of ED.
- Patients of ED who are not on any prior treatment.

Exclusion Criteria

- Prior treatment for ED.
- Staying for the next 4 months at a specific address.
- Accessible on the phone if unable to visit the hospital.
- IHD (Ischemic Heart Disease).
- Penile anatomical abnormalities.
- Spinal cord injury.
- Substance abuse.
- Taking nitrate compounds or androgens.
- History of adverse reaction to tadalafil.
- Comorbidity.
 - a. Uncontrolled HTN (Hypertension).
 - b. Psychological issues.
 - c. CNS (Central Nervous System) defect.
 - d. HIV (Human Immunodeficiency Virus).
 - e. CRF (Chronic Renal Failure).
 - f. Hepatic dysfunction.
 - g. CYP 450 inhibitors.

Patients presenting to urology OPD with ED diagnosed based on detailed history were included in the study after a complete evaluation of history of addiction such as alcoholism and smoking or use of any drugs which can affect sexual function of patient. At the time of examination patient's general examination was completed, blood pressure, respiratory rate, heart rate, complete blood count, liver and kidney function tests, and urine routine and culture sensitivity were done, ECG obtained, and later pre-treatment IIEF score was calculated. Detail physical examination for anatomical abnormality, phimosis, hypospadias, and previous surgery history was taken. Outpatients were randomized into two groups using the odd-even method. Before starting treatment, IIEF scoring was done for both groups. The Group 1 was given once-daily 5 mg tadalafil. Group 2 was given 10 mg tadalafil before sexual activity. Patient under study assessed at 4th week and 16th week.

We used IIEF questionnaire to assess the effect of treatment. In this questionnaire question number 1 - 5 and question 15 deal with erectile function of patient, question number 9 and 10 tells about orgasmic function, question 11, 12 about sexual desire and 6, 7 and 8 talks about intercourse satisfaction. Question number 13 and 14 tells overall satisfaction. This questionnaire applied to all patients before

start of treatment, at 4th week, and at 16th week. All questionnaire was filled by same person and patient and physicians were blind folded. Scoring scale is 1 to 30 which is divided into five groups of severe, moderate, mild to moderate, mild, and no dysfunction for score of 0 - 10, 11 - 16, 17 - 21, 22 - 25 and 26 - 30 respectively. Patients from the IIEF score of more than 25 were excluded from the study. We explained entire study process to patient in his language of understanding and only after that written informed consent was taken.

The statistical analysis is carried out using (SPSS) Statistical Package for the Social Sciences, version 13, and the Shapiro-Wilk test was used to check normalcy among both group. The results are given as mean $\pm$ standard deviation, n (%), paired t-test used for parametric data. Chi-square tests is for categorical variances. In all cases, p values less than 0.05 were defined as statistically significant.

RESULTS

One hundred and ten (110) patients were included in the study and were randomized into two groups of 55 each. Group 1 = tadalafil 5 mg daily dose regimen group. Group 2 = tadalafil 10 mg on-demand group. The mean age group of group 1 is 47.6 yrs. and group 2 is 49.6 yrs. In group 1, 19 patients are in the 30 - 45 age group, 18 from the 46 - 55 yrs. age range, 18 in the 56 - 65 age range. Group 2, 20 patients from the 30 - 45 age range, 15 from 46 - 55 age range, 20 from 56 - 65 age range. Age group difference in group 1 and 2 shows a p-value of 0.8172, statistically not significant. Patients with tadalafil 5 mg daily group had 2 (3.6 %) patients with mild symptoms, 25 (45.5 %) had mild to moderate symptoms, 28 (51 %) had moderate symptoms. No patient with a severe score (0 - 6) in the baseline was found in the study. Patients in group 2 (on-demand group) 35 (63.6 %) patients belong to a mild to moderate group, 20 (36.4 %) patients had a moderate IIEF score. The mean baseline score of group 1 is 12.84 ± 3.69 and group 2 has a mean baseline score of 13.18 ± 3.295 . Baseline score of groups 1 and 2 doesn't show statistically significant difference with P value 0.652, this shows the group is comparable. After 4 weeks mean IIEF score of group 1 increased to 15.55 ± 3.967 and group 2 score increase to 15.11 ± 3.32 . The difference in mean score at end of 4 wks.; In group 1 was 2.71 and group 2 was 1.93. This shows a statistically significant difference in tadalafil daily group vs. tadalafil on-demand group at end of 4 wks. With P-value 0.017. Group 1 shows 21.12 %, and group 2 shows a 14.64 % improvement in a score at the end of 4 weeks. Both showing statistically significant improvement compared to baseline in individual groups.

After 16 weeks, group 1 mean IIEF score was 18.24 ± 4.29 whereas group 2 score increased to 15.91 ± 3.014 . The difference in mean score from the baseline score after 16 weeks was 5.40 ± 2.55 for group 1 and 2.73 ± 1.096 for group 2. Improvement in IIEF from baseline shows statistically significant difference intragroup and intergroup study p-value 0.006.

Age Group (Yrs.)	Tadalafil 5 mg Daily	Tadalafil 10 mg On Demand	P-Value
30 - 45	19	20	0.817
46 - 55	18	15	
56 - 65	18	20	

Table 2. Age Distribution

	Normal	Mild	Mild to Moderate	Moderate	Severe
Baseline	0	2 (3.6 %)	25 (45.5 %)	28 (51 %)	0
4 th Week	0	11 (20 %)	34 (61.8 %)	10 (18.2 %)	0
12 th Week	3 (5.5 %)	16 (29.1 %)	32 (58.2 %)	4 (7.3 %)	0

Table 3. Group 1 (5 mg Tadalafil Daily)

	Normal	Mild	Mild to Moderate	Moderate	Severe
Baseline	0	0	35 (63.6 %)	20 (36.4 %)	0
4 th week	0	6 (10.9 %)	34 (61.8 %)	15 (27.3 %)	0
12 th week	0	10 (18.2 %)	33 (60 %)	12 (21.8 %)	0

Table 4. Group 2 (10 Mg Tadalafil On-Demand)

Scores	Group 1 Mean $\pm$ SD	Group 2 Mean $\pm$ SD	Z Value	P-Value
Baseline Score	12.84 $\pm$ 3.696	13.18 $\pm$ 3.295	- 0.451	0.652
4week Score	15.55 $\pm$ 3.967	15.11 $\pm$ 3.32	- 0.084	0.933
Difference in Score	2.71 $\pm$ 2.208	1.93 $\pm$ 0.920		
Improvement	21.12 %	14.64 %		
Paired t Test	- 9.098	- 15.535		
P Value	< 0.0001	< 0.0001		

Table 5. Comparison of Scores before and after 4 Weeks of Treatment among Groups

Scores	Group 1 Mean $\pm$ SD	Group 2 Mean $\pm$ SD	Z Value	P-Value
Baseline Score	12.84 $\pm$ 3.696	13.18 $\pm$ 3.295	- 0.451	0.652
4week Score	18.24 $\pm$ 4.299	15.91 $\pm$ 3.014	- 2.754	0.006
Difference in Score	5.40 $\pm$ 2.550	2.73 $\pm$ 1.096		
Improvement	42.05 %	20.71 %		
Paired t Test	- 15.703	- 18.448		
P Value	< 0.0001	< 0.0001		

Table 6. Comparison of Scores before and after 16 Weeks of Treatment among Groups

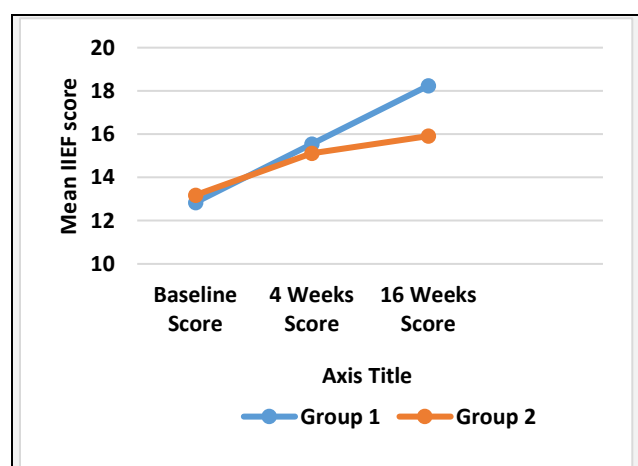
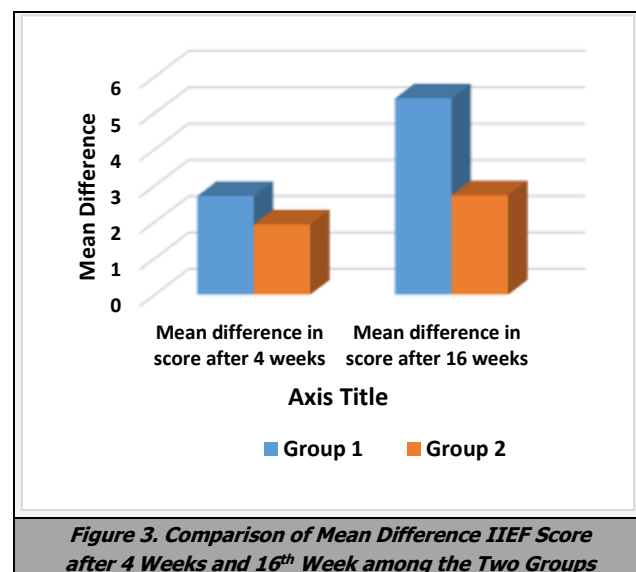


Figure 2 Comparison of Erectile Scores before and after Treatment among the Two Groups

Tadalafil 5 mg daily group shows 42.05 % improvement whereas tadalafil on-demand shows a 20.71 % improvement in score. Out of 28 moderate groups of Group 1, 24 showed improvement in score and only 4 remained in the same group. A total of 3 (5.5 %) patients in the daily tadalafil group return to normal. Of 20 patients from group 2 who

had a baseline score in moderate group 8 showed improvement in IIEF score and the remaining 12 remained in moderate group.

Figure 3. Comparison of Mean Difference IIEF Score after 4 Weeks and 16th Week among the Two Groups

DISCUSSION

Among all phosphodiesterase 5 (PDE 5) inhibitors, tadalafil is reversible, selective, and a potent inhibitor. Mechanism of action of PDE 5 inhibitor is to cause smooth muscle cell relaxation and vasodilation by increasing level of cGMP (Cyclic Guanosine Monophosphate).¹¹ In order to attain and maintain penile erection Corpora Cavernosum (CC) muscle plays important role, vasodilatation of CC leads to increase in blood flow in CC which lead to penile erection, PDE5 receptor present in abundance in CC and tadalafil act on it to cause its effect.¹² Tadalafil is extremely safe and effective and it has been proven in various studies.¹³ Tadalafil initially approved for low dose of 2.5 mg or 5 mg, but there has been various studies where 10 mg and 20 mg tadalafil has been effectively studied for erectile dysfunction treatment. Tadalafil has half-life of 17.5 hrs., so that makes it good agent for once a daily usage to provide steady supply.¹³ This has longer half-life than all other available PDE5 inhibitors. This property of tadalafil makes it suitable and provides a wide window to engage in sexual intercourse. It also allows the patients of erectile dysfunction to choose once-a-day dosing regimen as an alternative to the conventional on-demand dosing regimen of tadalafil and hence patient satisfaction.¹⁴ Although on-demand PDE5 inhibitors are also proven to be similarly effective in management of ED, but due to varied sexual patterns and timing this makes cumbersome for patient to taken on demand and lead to decrease compliance to drugs and overall decrease in scoring.¹⁴ Dosing option should be such that it eliminates the need and coordination of dosing and sexual activity which interim increase the compliance to drug. Pattern of sexual activity is very complex process which has multiple dimensions, varied behaviour complexity of sexual activity.¹⁵

Study	Study Design	Patient Population	No. of participants in the On-Demand Group	No. of Participants in Daily Group	On-Demand Dosage	Daily Dosage	Length of Follow-Up	Outcome Scores
McMahon 2005 ²⁰	RCT	Mild to severe ED	70	75	10 mg	10 mg	12 Weeks	IIEF-EF, SEP2 & 3, GAQ, TPQ
Kang et al 2012 ²¹	RCT	Mild to severe ED	68	66	20 mg	5 mg	4 weeks, 12 weeks	IIEF-EF (5), SEP2&3, GAQ
Jamshidian et al 2012 ¹⁹	RCT	ED only	50	50	10 mg	10 mg	12 wks., 24 weeks	IIEF-EF
Bolat et al 2018 ¹⁸	RCT	ED with DM	32	31	20	5 mg	12 weeks	IIEF-EF,EHS

Efficiency of Tadalafil Daily Versus on Demand Dosage Randomised Control Trials

Name of Study		On-Demand Group Mean IIEF-EF Score (SD)	Daily Group Mean IIEF-EF Score (SD)
McMahon ²⁰	Baseline	14.3 (4.71)	14.9 (5.15)
	12 weeks	23.3 (6.7)	26.4 (4.47)
Kang et al	Baseline	11.04 (4.8)	11.28 (4.9)
	12 weeks	16.92 (6.2)	19.08 (6.2)
Jamshidian et al(2012) ¹⁹	Baseline	13.48 (2.86)	12.64 (2.92)
	12 weeks	14.47 (3.25)	15.24 (3.56)
Bolat et al	Baseline	12.8 ± 5.7	12.6(6.8)
(2018) ¹⁸	12 weeks	15.1 ± 5.4	15.6 ± 7.2

Change in IIEF-EF Score in Daily Versus On-Demand Tadalafil Group

There have been several studies conducted for ED particularly in the field of daily dosing vs. on-demand dosing.^{16–19} The novelty about our study is on-demand 10 mg dose is being compared to 5 mg daily dosage.

McMahon et al (2005)²⁰ did a randomized cross over trial of daily tadalafil 10 mg vs. on demand 20 mg among 145 patients. He compared outcome after 12 weeks. He found baseline IIEF score increase from 14.6 to 23.3 in on demand group whereas in daily group this increase is 26.4. SEP 3 (Sexual Encounter Profile Question 3) shows positive response in both groups, from 30 % at baseline it increased to 67 % in on demand group and 80 % in daily group. There is statistically significant difference in preference of dosage only 28 % people preferred on demand dosage whereas 72 % preferred daily dosage.

A study by Kang et al²¹ they studied 168 patients of whom 134 completed study. They compared on demand 20 mg vs. daily 5 mg dosage and found 81% people from on demand continued study and only 78.6 % of daily dosage could continue study. IIEF score improvement was seen to be better in daily tadalafil group compared to on demand group showing improvement in score of 6.5 (4.5) and 4.9 (4.2) respectively which is statistically significant difference P value 0.035.

Our study also shows promising results in daily tadalafil 5 mg group, shows a statistically significant difference in tadalafil daily group vs. tadalafil on-demand group at end of 4 wks. With p-value 0.017. Group 1 shows 21.12 %, and group 2 shows a 14.64 % improvement in a score at the end of 4 weeks. The difference in mean score from the baseline score after 16 weeks was 5.40 ± 2.55 for group 1 and 2.73 ± 1.096 for group 2. Improvement in IIEF from baseline shows statistically significant difference intragroup and intergroup study p-value < 0.0001. Tadalafil 5 mg daily group shows 42.05 % improvement whereas tadalafil on-demand shows a 20.71 % improvement in score. These results are comparable to landmark studies and strengthen the daily dosage protocol use.

CONCLUSIONS

Tadalafil 5 mg once a day shows significant improvement in sexual function, and satisfaction when compared to tadalafil 10 mg on demand. Although both are effective in treatment of ED, its daily dosage is preferable compared to on-demand. With proper pre-treatment counselling, we can achieve almost zero dropout rate which goes a long way in treating ED.

Limitations

No long term follow up for side effects was included in the study.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.

Financial or other competing interests: None.

Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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