Tadalafil Improves Erectile Dysfunction and Quality Of Life in Men with Cirrhosis: A Randomized Placebo Controlled Trial

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Abstract

Background and Aims: Patients with cirrhosis have high prevalence of erectile dysfunction (ED). The aim of this study was to study the efficacy and safety of tadalafil for ED in patients with cirrhosis.

Methods: 140 cirrhotic males with ED were randomized into tadalafil 10 mg daily (n = 70) or placebo (n = 70) for 12 weeks. ED was diagnosed if erectile function (EF) domain score was < 25 in International Index of Erectile Function (IIEF) questionnaire. Primary outcome was proportion of patients having an increase in > 5 points in EF domain of the IIEF.

Results: At end of 12 weeks, more patients in tadalafil group achieved > 5 points increase in the EF domain of the IIEF as compared to the placebo group [44(62.9%) vs. 21(30%), $P < 0.001$]. At the end of 12 weeks, patients receiving tadalafil had significantly more change in scores on the erectile function domain, orgasmic function domain, intercourse satisfaction domain, overall satisfaction domain, erection vaginal penetration rates and successful intercourse; significantly more decline in the GAD-7 and PHQ-9 scores; significantly more improvement in scores of five of the eight domains of SF-36 (general health perception, vitality score, social functioning, role emotional, and mental health), and the mental component summary rates as compared to placebo. The development of side effects and the changes in HVPG were not significantly different between the two groups.

Conclusions: Tadalafil therapy significantly enhanced erectile function, improved anxiety, depression and quality of life, and was well tolerated by cirrhotic men with ED.

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Introduction

Erectile dysfunction (ED) is defined as the inability to attain or maintain a penile erection of sufficient quality to permit satisfactory sexual intercourse [1]. Patients with cirrhosis have high prevalence of ED (25–92%) [2–10]. Possible contributing factors to ED in cirrhosis patients include presence of co-morbidities and risk factors known to be involved in the development of ED (like hypertension, diabetes, metabolic syndrome, alcohol use, depression); and HCV infection [11]. Cirrhosis itself may favor ED development, possibly due to alterations of the sexual hormones metabolism, malnutrition and the frequent use of drugs potentially acting on penile erection, such as non-selective beta-blockers (NSBBs) and diuretics [6, 12].

It has been shown in patients without cirrhosis, that ED can have a negative effect on the quality of life in males. ED can cause psychological issues, like lower emotional satisfaction and general happiness [13]. ED has also been found to be associated with depressive symptoms [14], and a poor health related quality of life (HRQOL) in patients with cirrhosis [6, 15].

In Penile erection there is a complex neurovascular coordination of hemodynamic events involving the interaction of nerves, neurotransmitters, striated and smooth muscle and tunica albuginea. Any alteration in the above mentioned components can lead to ED. Oral drugs [phosphodiesterase type 5 (PDE-5) inhibitors], psychogenic counseling, vacuum device, vasoactive drug injections, transurethral drug therapy, vascular surgery and penile implants are some of the treatment options presently used for ED [16]. Patients generally have preference for oral drugs. A PDE-5 inhibitor blocks the degrading action of PDE-5 on cyclic guanosine monophosphate (c GMP) in the smooth muscle cells lining the blood vessels supplying the corpus cavernosum of the penis. These drugs are considered the first line treatment of ED [1].

Tadalafil is a PDE-5 inhibitor with half-life of 17.5 hours in normal healthy men, and the extended plasma half-time of tadalafil as compared to other PDE-5 inhibitors provides a longer therapeutic effect (up to 36 h). The longer half-life provides a steady state of serum drug concentration with low dose, once-daily administration [17]. The metabolism of tadalafil is via the hepatic enzyme cytochrome P450 3A4 (CYP3A4) to a catechol metabolite [17]. Tadalafil is excreted largely as metabolites, approximately two-thirds into the faeces and one-third into the urine [18]. In clinical pharmacology studies, tadalafil exposure in subjects with mild or moderate hepatic impairment (Child-Pugh Class A or B) was comparable to exposure in healthy subjects when a dose of 10 mg was administered. There are no available data for doses higher than 10 mg of tadalafil in patients with hepatic impairment. Insufficient data are available for subjects with severe hepatic impairment (Child-Pugh Class C) [18].

The effect of PDE-5 inhibitors on portal hemodynamics in patients with cirrhosis and portal hypertension in humans remain controversial. Acute variceal bleeding has been described after intake of 25 mg sildenafil [19, 20]. Studies have shown no significant acute (at 60–80 minutes) changes in HVPg after a single oral dose of 25 mg or 50 mg sildenafil [21–23]. On the other hand vardenafil (10 mg single oral dose in patients with Child A cirrhosis), decreased the hepatic vein pressure gradient (median reduction 16%) 1 hr after the dose [24]; and also udenafil (75–100 mg daily in Child A/B patients with cirrhosis) decreased HVPg (decrease by 15.7% from day 0 pre-dose to day 6 post-dose) [25]. Also, tadalafil 10 mg single oral dose in patients with cirrhosis did not significantly change the portal vein velocity and portal flow volume but significantly reduced the MAP and SVR 2 hrs after dose [26]. And a case report of a Child A patient with cirrhosis and recurrent bleeding from esophageal and rectal varices, treated with long term tadalafil 5 mg daily for 8 years, found beneficial portal hemodynamics effects and no bleed recurrence [26].

The physical activity, which often is required to engage in sexual activity, may itself slightly increase the HVPg. However, in patients receiving propranolol, HVPg did not increase during exercise, but decreased, possibly related to a more pronounced decrease in hepatic blood flow (as compared with patients receiving placebo), and to a blunted increase in cardiac output [27]. The effects of long term hepatic hemodynamic effects of tadalafil use in patients with cirrhosis treated for ED are unknown.

Tadalafil has been found to be useful as an oral therapy for mild-to-severe ED of psychogenic, organic, or mixed etiology [28]. There is paucity of data on use of tadalafil for ED in patients with cirrhosis. One previous uncontrolled study on 25 patients with cirrhosis and ED, administration of 10 mg tadalafil daily for 4 weeks, lead to significant improvement in erectile function as compared to baseline [2]. Also there is lack of data on effect of tadalafil in patients with cirrhosis and ED on quality of life and depression.

The aim of this study was to assess the efficacy and safety of tadalafil in men with cirrhosis and ED.

Materials And Methods

Trial design

This was a single centre randomized placebo controlled trial.

Participants

The study was conducted in the Department of Hepatology and Liver Transplantation, Institute of Liver and Biliary Sciences (ILBS), New Delhi from 30 June 2018 to 28 December 2019. The study was conducted on patients attending outpatient department or day care (for endoscopy or hepatic hemodynamic studies) of Department of Hepatology. The study was approved by the ILBS Institutional Review Board (Number: IEC/2018/60/MA04).

Patients who fulfilled the following inclusion criteria were eligible to participate in the study: male patients, age from 21 years to 60 years; Child's Grade A or B cirrhosis (CTP score up to 9) of any etiology; a minimum 3-month history of ED; a stable monogamous relationship with a female partner and anticipate having same adult female sexual partner during the study; and Karnofsky performance status of $\geq 70\%$.

After the screening visit, eligible candidates qualified for randomization by making at least four attempts at sexual intercourse during a 4-week treatment free run-in phase to determine baseline erectile function. They should also agree to make at least 1 sexual intercourse attempt per day with the female partner during days 1–4 following randomization (with a minimum of three attempts required during that period). Also agree to make at least 3 intercourse attempts during days 5–14 following randomization.

Following beta-blocker therapy was allowed: carvedilol (up to the max. dose of 25 mg) and propranolol (up to the max. dose of 160 mg). Patients were included if they were not on beta-blocker or on a stable dose of beta-blocker for at least last 6 weeks (beta-blocker dose was not modified during the duration of the study). Patients with history of endoscopically diagnosed large esophageal varices without previous bleeding were included if they were on a stable dose of prophylactic beta blocker for at

least last 6 weeks (beta-blocker dose was not modified during the duration of the study) or on endoscopic band ligation sessions (should have small esophageal varices at the time on enrollment in the study, and the last endoscopic band ligation session at least > 1 week ago). Patients with history of variceal bleeding were included if they bled > 4 weeks ago and were on secondary prophylaxis with endoscopic band ligation (should have small esophageal varices at the time on enrollment in the study, and the last endoscopic band ligation session at least > 1 week ago) and beta-blockers were continued if they were using them (beta-blocker dose was not modified during the duration of the study).

Exclusion criteria were the following:

1. Patients with overt hepatic encephalopathy; CTP score ≥ 10 ; history of variceal bleeding within last 4 weeks [patients were included if they bled > 4 weeks ago and were on secondary prophylaxis with endoscopic band ligation(should have small esophageal varices at the time on enrollment in the study, and the last endoscopic band ligation session at least > 1 week ago) and beta-blockers were continued if they were using them (beta-blocker dose was not modified during the duration of the study). ; and hepatocellular carcinoma; acute decompensated state of cirrhosis like gastrointestinal bleed/increased jaundice, active infection; post TIPS patients; acute febrile illness; and no consent.
2. Patients with HbA1c > 13.0% at the screening visit (visit 1, week - 4); a recent history of diabetic ketoacidosis (≥ 2 episodes), or ≥ 3 episodes of hypoglycemia requiring assistance. However, men with micro vascular complications, including retinopathy, were eligible.
3. Patients with history of angina during intercourse, unstable angina, or any other evidence of recently diagnosed coronary artery disease; poorly controlled blood pressure (systolic > 170 or < 90mm Hg or diastolic > 100 or < 50 mmHg) or orthostatic hypotension; arrhythmia, uncontrolled congestive heart failure; renal or respiratory failure; uncontrolled thyroid disorders and hemoglobin < 7.0.
4. Men who failed to achieve an erection after radical prostatectomy or pelvic surgery; those who had penile implants, clinically noteworthy penile deformities, or a history of psychiatric disorders, stroke or spinal-cord trauma within 6 months of study onset; those who were receiving nitrates, antiandrogens, antidepressant, anticonvulsants, other hypnotics or cancer chemotherapy; and patients with active alcohol/substance intake or intake within 1 month of enrollment.
5. Patients with history of hypersensitivity to the trial drugs or to drugs with a similar chemical structure.
6. Patients with Karnofsky performance status of below 70%.

Interventions: After the screening visit, eligible candidates qualified for randomization by making at least four attempts at sexual intercourse during a 4-week treatment free run-in phase to determine baseline erectile function. Participants were randomly allocated to one of two 12-week treatment arms: tadalafil 10 mg (n = 70) or placebo (n = 70)

Men were instructed to take one dose of their treatment at any time before anticipated sexual activity on days with anticipated sexual activity and daily at night after meals on days with no anticipated sexual activity.

Baseline and follow-up assessments:

Baseline assessment: Both the group of patients underwent the following investigations at baseline: History and physical examination, complete hemogram, renal function tests, serum electrolytes, liver function tests including INR, 12-lead electrocardiogram (ECG), urinalysis, etiological workup for cirrhosis as needed, ultrasound abdomen with Doppler splenoportal axis and hepatic veins, blood sugar fasting, HbA1c, alpha fetoprotein (AFP), serum thyroid stimulating hormone (TSH), serum sex hormone binding globulin (SHBG), serum testosterone (free and total), serum prolactin, serum luteinizing hormone (LH), serum follicle stimulating hormone (FSH), serum c-reactive protein (CRP), and chest X-ray.

Questionnaires assessment with Karnofsky Performance Score (KPS), International Index of Erectile Function (IIEF) questionnaire, Sexual Encounter Profile (SEP) diaries, quantitative Androgen Deficiency in the Aging Male (ADAM) questionnaire, Patient Health Questionnaire (PHQ-9), Generalized Anxiety Disorder 7 (GAD-7) questionnaire, and SF-36 questionnaire was also done at baseline. Nutritional assessment [by body mass index (BMI), bioelectrical impedance (BIA) and whole body Dual-energy X-ray absorptiometry (DXA)] and hepatic venous pressure gradient (HVPG) (only for patients posted for HVPG measurements, no HVPG was done specifically for this protocol) was also done at baseline.

Assessments at 4 and 8 weeks

History and physical examination, complete hemogram, renal function tests, serum electrolytes, liver function tests including prothrombin time and INR, Sugar (f), HbA1c.

Assessments at 12 weeks

History, physical examination, complete hemogram, renal function tests, serum electrolytes, liver function tests including INR, 12-lead ECG, urinalysis, blood sugar fasting, HbA1c, serum TSH, SHBG, serum testosterone (free and total), serum prolactin, serum LH, serum FSH, and serum CRP. Questionnaires assessment with KPS, IIEF questionnaire, SEP diaries, quantitative ADAM questionnaire, PHQ-9 questionnaire, GAD-7 questionnaire, SF-36 questionnaire; nutritional assessment and HVPg measurement was also done at week 12.

The effects of tadalafil on erectile function were evaluated using the IIEF questionnaire, SEP diaries and Global Assessment Question (GAQ).

The patients completed the IIEF at the conclusion of the run-in period (baseline) and after 12 weeks of double blind therapy. They completed the SEP diary after each sexual encounter and reviewed the diary with the physician at each visit. The patients completed the GAQ at the final visit (study end or early discontinuation).

Patients were monitored for side effects of drugs and complications at each visit.

Outcomes

Primary outcome measure was proportion of patients achieving more than a five-point gain from baseline to end point (at end of 12 weeks) in the erectile function domain of the IIEF.

Other secondary outcome measures studied included:

1. Changes from baseline to end point in scores on the following domains of IIEF: erectile function domain, orgasmic function domain, sexual desire domain, intercourse satisfaction domain, and overall satisfaction domain.
2. Change from baseline to end point in the proportion of patients achieving a final IIEF erectile function domain score of at least 26 (normal erectile function according to Cappelleri et al [29]).
3. Changes from baseline to end point in proportions of "yes" responses to 2 yes/no questions in the SEP diary: "Were you able to insert your penis into your partner's vagina?" (SEP-Q2) and "Did your erection last long enough for you to have successful intercourse?" (SEP-Q3 i.e. absolute proportion of successful intercourse completion among all sexual attempts)
4. Absolute proportion of affirmative responses to the GAQ 1 ("Did the treatment improve your erections?") and GAQ 2 (If yes to GAQ1, "Did the treatment improve your ability to engage in sexual activity?").
5. Changes from baseline to end point in q ADAMS, PHQ-9, GAD-7, and SF-36 scores.
6. Effect on HVPg [in the subgroup of patients who underwent HVPg measurements at baseline (and had HVPg > 10 mm Hg)] at end of 12 weeks, and
7. Side effects of the treatment.

Randomization: Random allocation sequence was done by computer generated random numbers code with an equal number of the alternative treatments. Patients were randomized to either of the two groups in 1:1 ratio.

Allocation concealment

Randomization was done with sequentially numbered, sealed envelopes using the previously determined code to either tadalafil or placebo. Sealed opaque thick papered envelopes were used to conceal the sequence until interventions were assigned.

Implementation

The computer generated random allocation sequence was generated by SK from the information technology department of the Institute; AB from the clinical research department of the Institute assigned participants to interventions (opened the sealed envelopes and assigned the subjects in either group as per randomization list); RKJ, MK and AB from Department of hepatology and liver transplantation enrolled participants in the study.

Blinding

Treatment and placebo pills were of similar size, shape and color. The participants, care providers, and those assessing outcomes were blinded. The code was not broken until the end of the study

Definitions and Study Assessments

Diabetes

A clinical diagnosis of diabetes was predicated on either current therapy with insulin, metformin, or sulfonylureas or a history within the previous year of two occasions of diagnostic-level hyperglycemia, including 1) fasting plasma, serum, or blood glucose > 7 mmol/l (126 mg/dl); 2) randomly obtained plasma, serum, or blood glucose $\geq$ 11.1 mmol/l (200 mg/dl) associated with symptoms of polyuria, polydipsia, or unexplained weight loss; or 3) plasma, serum, or blood glucose $\geq$ 11.1 mmol/l (200 mg/dl) 2 h after administration of 75 g oral glucose. Any patient with an onset of diabetes before the age of 30 years who had received continuous insulin treatment since diagnosis was considered to have type 1 diabetes.

Karnofsky Performance Score (KPS)

The Karnofsky Performance Score (KPS) ranking ranges from 100 to 0, where 100 is "perfect" health and 0 is death [30].

International Index of Erectile Function (IIEF), Sexual Encounter Profile (SEP) and Global Assessment Question (GAQ): The effects of tadalafil on erectile function were evaluated using the IIEF questionnaire, SEP diaries and GAQ. IIEF is a 15-item questionnaire that assesses five domains of male sexual function using 5- to 6-point Likert scales, with 0 or 1 signifying a low frequency or ability and 5 signifying a high frequency or ability [31]. These domains include erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. The erectile function domain consists of six questions concerning erection frequency, erection firmness, frequency of partner penetration, frequency of maintaining erection after penetration, ability to maintain erection to completion of intercourse, and confidence in achieving and maintaining erection. The erectile function domain possible scores range from 1 to 30. Severity of ED was defined using the IIEF-EF domain score: 5 or lower (no attempts at intercourse); 6 to 10 (severe ED); 11 to 16 (moderate ED); 17 to 25 (mild ED); and 26 to 30 ("normal" erectile function i.e. absence of ED). IIEF has been validated in the Indian population also [32].

Patients also used Sexual Encounter Profile (SEP) diaries, which are immediate recall instruments which allow the patients to document each sexual attempt during the course of the study. The percentage of 'yes' responses to the following SEP questions were assessed in this analysis: SEP2 "Were you able to insert your penis into your partner's vagina?" and SEP3 "Did your erection last long enough for you to have successful intercourse?".

In addition, at study end point or early discontinuation, each patient was asked two global assessment questions (GAQ 1 and 2). These questions were presented to patients at the last visit of the study and asked "whether treatment improved their erections" (GAQ1) (yes/no); and, if so, "whether treatment improved their ability to engage in sexual activity" (GAQ2) (yes/no).

Quantitative ADAM questionnaire

The qADAM questionnaire consists of the 10 questions on a Likert scale of 1–5, in which 5 represents the absence of a given symptom and 1 represents maximal symptoms. All questions are weighted equally. The summation of these responses yields a total qADAM score between 10 and 50, with 10 being most symptomatic and 50 being least symptomatic [33].

Generalized Anxiety Disorder 7 (GAD-7) questionnaire

GAD 7 is a self-reported questionnaire for screening and severity measuring of generalized anxiety disorder (GAD). The GAD-7 score is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of 'not at all', 'several days', 'more than half the days', and 'nearly every day', respectively, and adding together the scores for seven questions. GAD-7 score of ≥ 10 indicated probable diagnosis of GAD [34].

Patient Health Questionnaire (PHQ-9)

The PHQ-9 is the depression module, which scores each of the nine DSM-IV criteria as "0" (not at all) to "3" (nearly every day). PHQ-9 score ≥ 10 was taken as indication of major depression [35].

Short Form (36) Health Survey

Assessment of health related quality of life (HRQOL) was done using the Short Form (36) Health Survey. SF-36(v2) is designed to measure the full range of health status and wellbeing by means of 36 multiple-choice questions. It measures 4 scales in the area of physical health (physical functioning, role-physical, bodily pain, general health) and 4 in the area of mental-health (vitality, social functioning, role- emotional and mental health). Two comprehensive indexes of HRQOL were also computed, physical component summary and mental component summary. The lower scores indicate more disability [36].

Nutritional assessment

Height was measured to the nearest centimeter using a wall mounted standing measure. Current weight was recorded to the nearest 0.1 kg. Dry body weight was estimated using published suggested adjustment for the degree of fluid retention and a dry BMI estimated [37]. Body composition analysis was done by bioelectrical impedance (BIA) for fat, muscle and hydration assessment [38, 39]; and whole body Dual-energy X-ray absorptiometry (DXA) was done for measurement of human body composition [40]. BIA appendicular skeletal muscle index (ASMI) and DEXA ASMI calculations were done using standard formulae [38, 39, 40].

Statistical methods

Data was processed using the software packages SPSS version 20.0. Data were expressed as mean $\pm$ S.D in case of normally distributed continuous variables and median (range) for continuous variables not normally distributed. Categorical variables were expressed as number (percentage). For comparison of categorical variables; chi-square and Fisher's exact tests were used. For comparisons of continuous variables, t-test for normally distributed continuous variables and Mann-Whitney test for continuous variables not normally distributed were used. Wilcoxon rank sum test for paired continuous data and McNemar test for paired categorical variables were used.

All analyses were conducted on an intention-to-treat basis. The analysis of efficacy included all

patients who had a baseline measurement and at least one post-baseline measurement. The analysis of safety included all randomized patients.

For each SEP question, baseline and post-baseline scores were percentage of yes responses relative to number of sexual encounters during the run-in period and the treatment period, respectively. Proportions of yes responses to SEP diary questions were treated as continuous variables. P value of less than 0.05 was said to statistically significant.

Sample size

There were no previous RCTs of tadalafil for erectile dysfunction in cirrhotics. Placebo response rate for increase more than five points in erectile function domain score was taken as 15%, as one trial on tadalafil in diabetics reported placebo response rates of 13% at 12 weeks [41]. Response rates in tadalafil group were assumed to be 40% as one study on tadalafil in diabetics reported increase of more than five points in erectile function domain score of 44% after 12 weeks of tadalafil 10 mg daily [41]. And one study in cirrhotics reported that 44% of patients had resolution of ED at 4 weeks of tadalafil 10 mg treatment [2].

Assuming that increase more than five points in erectile function domain score would be 40 % with tadalafil and 15% with placebo, with alpha 5% and power 80% we needed to enroll 114 cases. Assuming defaulter rate to be 20 % it was decided to enroll total 140 cases (70 cases in each group). No interim analysis was planned.

Results

Participant flow and Numbers analyzed: The study was conducted from 30 June 2018 to 28 December 2019. In all 400 patients with cirrhosis were screened (Figure 1). Finally 140 patients who fulfilled the inclusion and exclusion criteria were randomized to the tadalafil arm (n=70) and placebo arms (n=70). Trial was stopped after achieving the required sample size.

Baseline data:

Table 1 shows the baseline demographic, clinical, hormonal, characteristics for each group. Table 1 also shows the baseline results of various questionnaires used in the study.

12 weeks of therapy was completed by all the patients in both the groups.

Effects on erectile function:

Effects of tadalafil on erectile function were evaluated using the IIEF questionnaire, SEP diaries and the GAQs (Table 2).

Proportions of patients achieving more than a five-point gain from baseline to end point (at end of 12 weeks) in the erectile function domain of the IIEF was significantly higher in tadalafil group as compared to the placebo group [44(62.9%) vs. 21(30%), $P<0.001$]. However, the proportions of patients achieving a final IIEF erectile function domain score of at least 26 (i.e. normal erectile function) was similar in both the groups [9/70(12.9%) in tadalafil group vs. 3(4.3%) in placebo group, $P=0.128$]. (Table 2)

At the end of 12 weeks, patients receiving tadalafil had significantly more change in scores on the erectile function domain ($P<0.001$), orgasmic function domain ($P=0.010$), intercourse satisfaction domain ($P=0.001$), overall satisfaction domain ($P=0.041$), erection vaginal penetration rates (SEP-Q2, $P<0.001$) and successful intercourse rates (SEP-Q3, $P<0.001$) as compared to placebo. But, the change in sexual desire scores was similar in both the groups ($P=0.188$) (Table 2).

The percentage of yes responses to GAQ1 ("Did the treatment improve your erections?") was 78.6% for the tadalafil group compared with 15.7% for placebo group ($P<0.001$). For GAQ2 ("Did the treatment improve your ability to engage in sexual activity?"), 70% of patients in the tadalafil group said 'yes' compared with 8.6% for placebo group ($P<0.001$).

Effects on scores of quantitative ADAM, GAD-7, PHQ-9 and SF-36 v2 questionnaires

At the end of 12 weeks, changes in q ADAM scores were similar in both groups, where as declines in the GAD-7 and PHQ-9 scores were significantly more in tadalafil group as compared to placebo ($P=0.022$ and 0.006 respectively) (Table 3)

At the end of 12 weeks, there were significantly more improvement in scores of, five general health perception, vitality score, social functioning, role emotional, and mental health) of the eight domains of SF-36, and the mental component summary in tadalafil group as compared to placebo (Table 3).

Effects on HVPG

At the end of 12 weeks, the changes in HVPG were not significantly different between the two groups. (Table 4).

Side effects of therapy

The development of side effects was similar in the two groups (Table 5). There were no serious adverse events.

Discussion

ED is a common problem in patients with cirrhosis with high prevalence (25–92%) [2–10]. ED can have a negative effect on the quality of life in males [6, 15]. ED can cause psychological issues (like less emotional satisfaction and general unhappiness [13]) and depression [14]. Tadalafil has been found to be useful as an oral therapy for mild-to-severe ED of psychogenic, organic, or mixed etiology [1].

There has been paucity of placebo controlled RCTs on efficacy and safety of tadalafil in patients with cirrhosis and ED. In this study, after 12 weeks of therapy, tadalafil significantly improved erectile function as compared to placebo in patients with cirrhosis and ED. Proportions of patients achieving more than a five-point gain from baseline to end of 12 weeks in the erectile function domain of the IIEF was significantly higher in tadalafil group as compared to the placebo group [44(62.9%) vs. 21(30%), $P < 0.001$]. At the end of 12 weeks, patients receiving tadalafil had significantly more change in scores on the erectile function domain, orgasmic function domain, intercourse satisfaction domain, overall satisfaction domain, erection vaginal penetration rates and successful intercourse rates as compared to placebo. One previous uncontrolled study on 25 patients with cirrhosis and ED, administration of 10 mg tadalafil daily for 4 weeks, lead to significant improvement in IIEF score as compared to baseline (15.08 vs 22.00, $P \leq 0.001$; overall increase in the IIEF scores was 6.9 ± 1.6), with 11 (44%) patients showing resolution of ED (i.e. IIEF score ≥ 25 at the end of 4 weeks of therapy [2].

In this study, at the end of 12 weeks, decline in the GAD-7 (measuring anxiety) and PHQ- 9 (measuring depression) scores were significantly more in tadalafil group as compared to placebo.

Few studies using tadalafil 5 mg for 8 weeks in non-cirrhotic patients with depression and ED, have found improvement in erectile function and depression [42, 43]. It has been found that brain-derived neurotrophic factor (BDNF) is involved in the pathophysiology of depressive disorder [44]. And the cyclic adenosine monophosphate response element binding protein (CREB) is one of the transcription factors that regulates BDNF expression [45]. Reduced CREB/BDNF signaling may contribute to the pathophysiology of depression and increasing CREB/BDNF signaling in depressive disorder might be one of the mechanisms underlying the effectiveness of PDE-5 inhibitors for the treatment of depression [46]. In addition, the improvement in depressive symptoms after treatment with PDE-5 inhibitors may also be explained by some other mechanism also. It may partly be explained by a corresponding improvement in self-confidence that follows the improvement of erectile function [47]. Whether the improvement in depressive symptoms after administering tadalafil was related to improvements in erection or a cerebral biological alteration requires further studies.

In this study, at the end of 12 weeks, there was significantly more improvement in scores of, five of the eight domains of SF-36 (general health perception, vitality score, social functioning, role emotional, and mental health), and the mental component summary in tadalafil group as compared to placebo. There is paucity of data on effect of tadalafil on quality of life parameters, when used for treatment of ED in patients with cirrhosis. In a recent study (single group, open-labelled, before-and-after preliminary trial) on South Korean men (without cirrhosis) with andropause symptoms, including ED, use of once-a-day 5mg dose of tadalafil for 8weeks, resulted in a significant increase in the sexual function, and a significant improvement in the mental component summary score of the SF-12 questionnaire (specifically increase in vitality, role emotional and mental health) at 8 weeks. Among the physical component summary sub items, only the change in general health perception was significant [48]. This improvement in quality of life appears to be related to an increase in self-confidence associated with improved sexual function and sex life, and improved partner relationship [48]. Another study with tadalafil use (5 mg daily for 12 weeks compared to placebo) among men (without cirrhosis) with ED significantly improved erectile function and sexual quality of life (in patients and their female partners) [49]. There are other studies in patients without cirrhosis and ED showing that, sildenafil use significantly improved key quality of life parameters related to sexual dysfunction (overall satisfaction with sex life, sexual relationships with partners, concerns about erectile problems) and general mental health (well-being, self-control, satisfaction with relationship, health relative to 1 year ago, mental health) [50]. The absence of improvement in physical component

summary, physical functioning, role physical and bodily pain in our study likely is due the fact that we have excluded patients with poor performance status.

In this study, at the end of 12 weeks, the changes in HVPg were not significantly different between the tadalafil and placebo groups. Animal studies have suggested that PDE-5 inhibitors may be risky to use in cirrhosis. In rats, phosphodiesterase type-5 is also present in the superior mesenteric artery [51]. Administration of sildenafil results in a dose-dependent increase in mesenteric blood flow and a minor increase in portal venous pressure, in both the bile-duct-ligated rat, as well as in control rats [52]. It has been suggested that phosphodiesterase type-5 is also present in human mesenteric arteries [53]. There is paucity of data on effects of long term PDE-5 inhibitors use on portal hemodynamics in patients with cirrhosis and portal hypertension in humans. Acute effects of PDE-5 inhibitors on portal hemodynamics also remain controversial. While no significant changes in HVPg were observed after acute use of sildenafil (25–50 mg single oral dose) [21–23]; verdenafil (10 mg single oral dose) [24], and udenafil (75–100 mg daily for 6 days) [25] significantly decreased HVPg. As far as tadalafil is concerned, one study found that tadalafil 10 mg single oral dose in patients with cirrhosis did not significantly change the portal vein velocity and portal flow volume 2 hrs after dose [26]. One case report of a Child A patient with cirrhosis and recurrent bleeding from esophageal and rectal varices, treated with long term tadalafil 5 mg daily for 8 years, found beneficial portal hemodynamics effects and no bleed recurrence [26]. Further long term larger studies are needed to evaluate long term portal hemodynamic effects of tadalafil in patients with cirrhosis especially when used for treating ED.

In this study, the development of side effects in the tadalafil treated patients were similar to the placebo treated patients. The chief adverse events were dizziness, bloating, mild headache and nasal congestion. In one previous uncontrolled study on 25 patients with cirrhosis and ED, administration of 10 mg tadalafil daily for 4 weeks, 3 patients reported adverse events (dyspepsia – 2, headache – 1). None of these were dose limiting [2]. In noncirrhotic patients treated for ED or benign prostatic hyperplasia, adverse effects noted in $\geq 2\%$ of patients included headache, dyspepsia, back pain, myalgia, nasal congestion, flushing, and pain in limb [18].

There are certain limitations of this study. This study was limited to 12 weeks, so, further long term larger studies are needed to evaluate side effects and long term portal hemodynamic effects of tadalafil in patients with cirrhosis. This study excluded patients with CTP score ≥ 10 and Karnofsky performance status of below 70%, so, the efficacy and tolerability of tadalafil in patients with advanced cirrhosis and poor performance status remains to be evaluated.

Conclusions

Tadalafil therapy significantly enhanced erectile function, improved anxiety, depression and quality of life; and was well tolerated by men with cirrhosis and ED.

Abbreviations

ASMI- Appendicular skeletal muscle mass index; **BIA**- bioelectrical impedance; **DEXA**- Dual-energy x-ray absorptiometry; **ED**- Erectile dysfunction; **GAD**- Generalized anxiety disorder; **IIEF**- International index of erectile function; **q** **ADAM**- Quantitative androgen deficiency in the aging male questionnaire; **PHQ**- Patient health questionnaire; **SEP**- Sexual Encounter Profile

Declarations

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Conflict of interest: None

Ethics approval and registration: The study was approved by the Institutional Review Board (IRB) of the Institute of Liver and Biliary Sciences, New Delhi, India, where the study was conducted (Institutional ethical committee number:

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Author contributions: RKJ, MK and SKS developed the protocol. RKJ, MK and AB enrolled participants in the study. SMS, AK, JB, RM, AJ, AC, VR, and VA reviewed and provided inputs to the protocol and manuscript. Guresh Kumar helped with statistical analysis and protocol development.

Data transparency: All data, materials and software applications support the published claims and comply with field standards.

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Tables

Table 1. Baseline characteristics of patients receiving tadalafil and placebo

Parameters	Tadalafil (n=70)	Placebo (n=70)	P value
Age (years), median (range)	44.3(28-58)	48(24-58)	0.066
Male sex, n (%)	70(100)	70(100)	1.000
Etiology of cirrhosis, n (%)			
Alcohol/ NASH /HBV/HCV/others	30(42.9)/24(34.3)/8(11.4)/4(5.7)/4(5.7)	33(47.1)/18(25.7)/9(12.9)/5(7.1)5(7.1)	0.865
Duration of cirrhosis diagnosis (months), median (range)	48(12-96)	48(12-96)	0.495
HR (per min), median (range)	66(56-90)	69(56-90)	0.230
MAP (mm Hg), median (range)	83(68-100)	83(71-103)	0.846
Hb ((g/dL), median (range)	9.8(7.0-15.3)	9.3(7.0-14.3)	0.329
TLC ((10 ³ cells/mm ³), median (range)	5.2(1.8-10.8)	5.7(2.1-12.0)	0.297
Platelet (10 ⁵ cells/mm ³), median (range)	74(25-175)	76(24-219)	0.537
Creatinine (mg/dL), median (range)	0.85(0.33-2.91)	0.8(0.04-2.91)	0.517
Serum sodium (meq/L), median (range)	134(124-145)	134(122-142)	0.310
Bilirubin(mg/dL), median (range)	1.35(0.25-9.9)	1.35(0.4-4.6)	0.642
AST(IU/L), median (range)	33(12-112)	34(12-89)	0.907
ALT(IU/L), median (range)	22(8-92)	22(9-70)	0.990
Serum albumin(g/L), median (range)	2.9(1.6-4.6)	2.7(1.5-4.1)	0.973
INR, median (range)	1.3(1-2)	1.4(0.8-3.1)	0.504
CTP score , median (range)	6(5-9)	6(5-9)	0.863
CTP class, n (%) A/B/C	39(55.7)/31(44.3)/0	40(57.1)/30(42.9)/0	1.00
MELD, median (range)	12(7-23)	12.5(7-24)	0.750
LSM (kPa) , median (range)	43.2(12.5-75)	43.6(10.5-75)	0.630
CRP(mg/L), median (range)	3(0.55-16.2)	3.2(0.3-64.4)	0.960
Ascites at presentation [yes/no], n (%)	5(7.1)/65(92.9)	4(5.7)66(94.3)	0.766
	5/5(100)/0/0	4/4(100)/0/0	1.00
Ascites grade in patients having ascites [1/2/3], n (%)			
Past h/o SBP, n (%)	12(17.1)	11(15.7)	1.00
Past h/o overt HE, n (%)	13(18.6)	8(11.4)	0.344

Past h/o AKI, n (%)	11(15.7)	5(7.1)	0.183
Past h/o variceal bleed, n (%)	18(25.7)	13(18.6)	0.416
History of UTI, n (%)	7(10)	7(10)	1.00
Baseline HVPg done in, n	37	30	
HVPg (mmHg) , median (range)	17(9-23)	16(11-24)	0.109
HVPg > 10 mm Hg, n (%)	36/37(97.3)	30/30(100)	1.000
HVPg > 12 mm Hg, n (%)	34/37(91.9)	27/30(90)	1.000
Hormonal Data			
Total testosterone(ng/dl) , median (range)	189.1(32.6-885)	187.2(14.3-886.3)	0.684
Free testosterone(pg/ml) , median (range)	7.7(0.55-50.60)	7.6(0.4-56.2)	0.558
LH(mIU/ml) , median (range)	4.3(1.1-10.2)	4.1(1.4-9.4)	0.142
FSH(mIU/ml) , median (range)	4.5(1.8-9.4)	4.3(1.5-10.2)	0.657
SHBG(nmol/L) , median (range)	79.5(17.8-245.8)	78.5(28.9-410)	0.830
Prolactin(ng/ml) , median (range)	12.8(2.9-90.1)	21.4(2.9-98)	0.359
AFP (ng/mL), median (range)	2.1(0.6-8.1)	2.1(0.6-8.2)	0.938
TSH (U/mL), median (range)	2.5(0.5-5.2)	2.5(0.6-5.2)	0.794
Medical history			
Hypertension, n (%)	8(11.4)	14(20)	0.254
Dyslipidemia, n (%)	8(11.4)	14(20)	0.254
Diabetes, n (%)	23(32.9); 72(12-240)	19(27.1);96(36-180)	0.580
Current diabetic therapy, n (%)	7/23(30.4)/12/23(52.2)/4/23(17.4)/0	2/19(10.5)/7/19(36.8)/10/19(52.6)/0	0.042
Insulin only/ Oral only/ Insulin+ oral/ None			
Coronary artery disease, n (%)	1(1.4)	0(0)	1.00
Hypothyroidism, n (%)	5(7.1)	3(4.3)	0.718
Concomitant medications for cirrhosis			
Beta-blockers, n (%)	61(87.1)	63(90)	0.791
Propranolol, n(%); Dose (mg/d) , median (range)	24/61(39.6);40(20-80)	26/63(41.3);30(20-80)	0.856
Carvedilol, n(%); Dose (mg/d) , median (range)	37/61(52.9);12.5(6.25-18.75)	37/63(58.7);12.5(6.25-12.5)	0.856

Diuretics, n (%)	36(51.4)	36(51.4)	1.00
Rifaximin, n (%)	21(30)	22(31.4)	1.00
Lactulose, n (%)	33(47.1)	35(50)	0.866
BCAA, n (%)	29(41.4)	31(44.3)	1.00
IIEF Questionnaire			
Total IIEF score, median (range) [Max 75]	23.5(5-57)	23.5(5-46)	0.882
IIEF erectile function domain score, median (range) [Max 30]	9(1-24)	9(1-22)	0.834
IIEF erectile function severity, n (%)	10(14.3)	7(10)	0.814
Mild (17–25)	20(28.6)	24(34.3)	
Moderate (11–16)	30(42.9)	30(42.9)	
Severe (6–10)	10(14.30)	9(12.9)	
No attempt at intercourse (≤5)			
IIEF orgasmic function domain score, median (range) [Max 10]	3(0-8)	2.5(0-6)	0.409
IIEF sexual desire domain score, median (range) [Max 10]	4(2-10)	4(2-10)	0.509
IIEF intercourse satisfaction domain score, median (range) [Max 15]	4(0-11)	4(0-9)	0.945
IIEF overall satisfaction domain score, median (range) [Max 10]	2(0-9)	2(0-9)	0.855
SEP-Q2 ("Were you able to insert your penis into your partner's vagina?"), n (%) #	25(0-42.8)	25(0-50)	0.373
SEP-Q3 ("Did your erection last long enough for you to	16.6(0-30)	16.6(0-40)	0.290

have successful intercourse?")@			
SF-36(v2) Questionnaire			
Physical functioning score, median (range)	75(20-95)	75(15-100)	0.898
Role physical score, median (range)	40(0-100)	40(0-100)	0.787
Bodily pain score, median (range)	55(12.5-100)	55(22.5-100)	0.582
General health perception score, median (range)	15(5-40)	15(5-60)	0.397
Vitality score, median (range)	50(5-70)	45(20-70)	0.330
Social functioning score, median (range)	43.7(12.5-87.5)	50(12.5-100)	0.443
Role emotional score, median (range)	55(0-100)	45(25-100)	0.182
Mental health score, median (range)	48(0-72)	48(24-76)	0.664
Physical component summary score, median (range)	37.5(15-60)	35(15-60)	0.672
Mental component summary score, median (range)	43(20-65)	40(20-65)	0.667
Other Questionnaires			
Karnofsky Performance score, median (range)	100(80-100)	100(80-100)	0.570
q ADAM score, median (range)	23(13-38)	23(13-45)	0.249

GAD-7 score , median (range)	9(2-20)	9(2-20)	0.877
GAD-7 score ≥ 10 , n (%)	33(47.1)	34(48.6)	1.00
PHQ-9 score , median (range)	9.5(2-26)	10(0-24)	0.667
PHQ-9 score ≥ 10 , n (%)	35(50)	36(51.4)	1.00
Nutritional and body composition parameters			
Height (cm), median (range)	168.5(155-183)	170.5(156.5-179)	0.458
Weight (kg), median (range)	74.9(47.5-116)	77.4(54.3-101)	0.400
BMI (kg/m ²), median (range)	26.5(16.4-40.6)	26.1(18.1-36.9)	0.692
DEXA T score , median (range)	-1(-2.9-1.5)	-1.1(-2.9-1.6)	0.778
DEXA ASMI(kg/m ²) , median (range)	8.3(5.2-11.7)	8.6(5.3-10.6)	0.701
BIA phase angle , median (range)	5.5(4-6.4)	5.5(3.7-6.3)	0.904
BIA ASMI(kg/m ²) , median (range)	8.1(5.3-11.4)	8.1(5.1-10.1)	0.728

Data are n (%) or median (range).

Percentages are median (range) per-patient percentages of yes responses to SEP2

@Percentages are median (range) per-patient percentages of yes responses to SEP3

Abbreviations: NASH- Nonalcoholic steatohepatitis; HBV-Hepatitis B virus; HCV-Hepatitis C virus; BMI- Basal metabolic rate; HR- Heart rate; MAP- Mean arterial pressure; Hb- Hemoglobin; TLC- Total leukocyte count; AST- Aspartate aminotransferase; ALT- Alanine aminotransferase; INR- *International normalized ratio*; CTP score- Child turcotte pugh score; MELD- Model for end-stage liver disease; LSM- Liver stiffness measurement; CRP- C –reactive protein; SBP- Spontaneous bacterial peritonitis; HE- Hepatic encephalopathy; AKI- Acute kidney injury; UTI- Urinary tract infection; HVPg- Hepatic vein pressure gradient; LH- *Luteinizing hormone*; FSH- Follicle-stimulating hormone; SHBG-Sex hormone binding globulin ; AFP- Alfa-feto protein; TSH- Thyroid stimulating hormone; Art. NH3- arterial ammonia; BCAA- Branched chain amino acids; IIEF- International index of erectile function; SEP- Sexual Encounter Profile; q ADAM- Quantitative androgen deficiency in the aging male questionnaire; PHQ- Patient health questionnaire; GAD- Generalized anxiety disorder; BMI- Body mass index; DEXA- Dual-energy x-ray absorptiometry; ASMI- Appendicular skeletal muscle mass index; BIA- bioelectrical impedance

Table 2. Effects on erectile function at 12 weeks of therapy in tadalafil and placebo groups

Parameters	Tadalafil (n=70)	Placebo (n =70)	P1 value
> 5-point gain in the erectile function domain of the IIEF, n (%)	44(62.9)	21(30)	<0.001
Patients achieving a final IIEF erectile function domain score of at least 26, n (%)	9(12.9)	3(4.3)	0.128
Δ IIEF erectile function domain(Q1,2,3,4,5,15), median(range)	7.5(-10- 21)	3.5(-7-16)	<0.001
Δ IIEF orgasmic function domain (Q9,10), median(range)	3(-3-9)	2(-3-5)	0.010
Δ IIEF sexual desire domain (Q 11,12), median(range)	2(-8-7)	1(-6-6)	0.188
Δ IIEF intercourse satisfaction domain (Q6,7,8), median(range)	5(-6-13)	3.5(-5-9)	0.001
Δ IIEF overall satisfaction domain (Q13,14), median(range)	3(-4-8)	2(-5-6)	0.041
Δ SEP-Q2 ("Were you able to insert your penis into your partner's vagina?"), n (%) #	35(0-58.3)	8.6(-5-30)	<0.001
Δ SEP-Q3 ("Did your erection last long enough for you to have successful intercourse?"), n (%) @	33.7(11.4-55.7)	11.1(-6.6-30)	<0.001
GAQ1 ("Did the treatment improve your erections?"), n (%)	55(78.6)	11(15.7)	<0.001
GAQ2 (If yes to GAQ1, "Did the treatment improve your ability to engage in sexual activity?"), n (%)	49(70)	6(8.6)	<0.001

Percentages are median (range) per-patient percentages of yes responses to SEP2

@ Percentages are median (range) per-patient percentages of yes responses to SEP3

Abbreviations: P1value: P value tadalafil vs placebo; P2value: P value baseline vs 4 weeks; IIEF- International index of erectile function; SEP- Sexual encounter profile; GAQ- Global assessment question

Table 3. Effects on scores of quantitative ADAM, GAD-7, PHQ-9 and SF-36 (v2) questionnaires at 12 weeks of therapy in tadalafil and placebo groups

Parameters	Tadalafil (n=70)	Placebo (n =70)	P value
Δ q ADAM score, median(range)	6(-7-29)	3(-4-20)	0.146
Δ GAD-7 score, median(range)	-3(-14-3)	-2.5(-14-4)	0.022
Δ PHQ-9 score, median(range)	-3(-13-2)	-2(-7-4)	0.006
SF-36(v2) Questionnaire			
Δ Physical functioning score, median (range)	5(-35-35)	5(0-40)	0.380
Δ Role physical score, median (range)	10(-40-30)	10(-20-60)	0.381
Δ Bodily pain score, median (range)	5.7(-22.5-27.5)	5(-2.5-27.5)	0.145
Δ General health perception score, median (range)	15(-5-35)	5(-10-25)	<0.001
Δ Vitality score, median (range)	20(0-35)	10(0-40)	<0.001
Δ Social functioning score, median (range)	17.5(-25-50)	6.2(0-25)	<0.001
Δ Role emotional score, median (range)	22.5(-45-75)	15(-40-75)	0.007
Δ Mental health score, median (range)	20(0-40)	10(-4-43)	<0.001
Δ Physical component summary score, median (range)	8.5(-5-24)	5(-15-25)	0.129
Δ Mental component summary score, median (range)	13.2(-5.5-39)	4.5(-0.5-24.5)	<0.001

Abbreviations: q ADAM: quantitative ADAM questionnaire; GAD-7: generalized anxiety disorder 7 (GAD-7) questionnaire; PHQ-9: patient health questionnaire; SF-36(v2): short form (36) health survey

Table 4. Effects on HVPg at 12 weeks of therapy in tadalafil and placebo groups

Parameters	Tadalafil (n=70)	Placebo (n =70)	P value
HVPg baseline mm Hg, median(range)	Available in 37 patients; 17(9-23)	Available in 30 patients; 16(11-24)	0.109
HVPg 12 weeks mm Hg, median (range)	Available in 19 patients; 15(9-19)	Available in 13 patients; 15(10-19)	0.623
Δ HVPg mm Hg, median(range)	-3(-8-3)	-2(-5-4)	0.323
HVPg decline ≥20% from baseline	6/19(31.6)	3/13(23.1)	0.704
HVPg decline ≥10% from baseline	17/19(89.5)	10/13(76.9)	0.374
HVPg ≤ 12 mm Hg at wk 12	3/19(15.8)	1/13(7.7)	0.629
HVPg ≤ 10 mm Hg at wk 12	2/19(10.5)	1/13(7.7)	1.000

Abbreviations: q ADAM: quantitative ADAM questionnaire; GAD-7: generalized anxiety disorder 7 (GAD-7) questionnaire; PHQ-9: patient health questionnaire; SF-36(v2): short form (36) health survey

Table 5. Side Effects of therapy in tadalafil and placebo groups

Side effects	Tadalafil (n=70)	Placebo (n=70)	P value
Dizziness without hypotension	6 (8.6)	1(1.4)	0.115
Mild headache	3(4.2)	0	0.244
Peroorbital swelling	2(2.8)	0	0.498
Nasal congestion	4(5.7)	2(2.8)	0.687
Itching	1(1.4)	0	1.00
Bloating	3(4.2)	9(12.8)	0.128

Figures

Figure 1

Participant flow in the study

Supplementary Files

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- [CONSORT2010Checklist.doc](#)