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Efficacy of Tadalafil on Lower Urinary Tract Symptoms of Patients with Ureteral Stents: A Study Protocol for a Randomized Controlled Trial

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Authors' contributions

This work was carried out in collaboration between all authors. Author AJ made the conception and design, acquisition of data, drafting of the manuscript, analysis and interpretation of data. Author SH made the conception and design, critical revision of the manuscript for important intellectual content, administrative, technical or material support and supervision. Author HSB analysis and interpretation of data and statistical analysis. Author AF acquisition of data and critical revision of the manuscript for important intellectual content. Author HB give the administrative, technical or material support. All authors read and approved the final manuscript.

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Study Protocol

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ABSTRACT

Objectives: Ureteral stenting is a common intervention in endourological procedures. Despite the usefulness of stents, patients may experience various stent-related symptoms. These symptoms can have a significant impact on patients' health related quality of life. There are several medical modalities for symptom improvement and Phosphodiesterase 5 Inhibitors are recent therapeutic option. This study is designed to evaluate the effects of Tadalafil on alleviation of stent associated symptoms measured by Ureteral Stents Symptom Questionnaire.
Design: In this Randomized Controlled Trail patients were randomly assigned to an intervention or Placebo group by a computer based random block design. Patients received encoded drug packages from a central call system. Physicians, patients and statistical analyzers were not aware of the designated intervention.
Setting and Conduct: Patients received treatment with Tadalafil or placebo for four weeks after ureteral stent insertion and completed a follow up session four weeks after the intervention.
Participants: Male patients who underwent unilateral ureteral stenting in Imam Reza hospital in Tabriz, Iran were enrolled in this study. Patients with history of hypertension, heart and/or respiratory disease, stroke, hypotension, renal failure, consumption of nitrate drugs and a positive urine culture or who had any allergic reaction to Tadalafil were excluded.
Interventions: Patients were allocated to receive Tadalafil 10 mg or Placebo daily for four weeks.
Outcome Variables: The primary outcome variables were stent related symptoms (urinary symptoms, pain, general health, sex and working status). Secondary outcomes included possible side effects such as cardiovascular, respiratory, gastrointestinal, musculoskeletal and central nervous system problems.

Keywords: Lower urinary tract symptom; quality of life; Tadalafil; ureteral stents.

1. INTRODUCTION

Inserting ureteral stents is one of the common interventions in endourological practice, which was first performed by Zimskind in 1967 [1]. Ureteral stents have been used extensively for urinary tract problems [2]. The double-J stent, most common indwelling ureteral stent, is utilized in obstructive pyelonephritis or uropathy, ureteral edema, intractable acute renal colic, iatrogenic ureteral damages following endoscopic procedures, and Stone Street (steinstrasse) [3].

Contrary to the stents advantageous, roughly 78% of patients have various stent-related symptoms such as pain (detected in 80% of patients), urinary frequency and urgency. These symptoms leads significant decline in health-related quality of life in 45-80% of patients [4]. Increased renal pelvis pressure during urination and irritation of trigon by the intravesicular curl of the stent can have considerable role in stent-related symptoms [5].

There are several medical modalities for stent-related symptom improvement. Pharmacologic interventions including alpha-1-blockers and antimuscarinic drugs were studied in various experiments [6-10]. Pharmacologic management is modest and noninvasive method. More invasive modalities include changing length or stent material and periureteral Botox injection. For this reason, several studies have been conducted to evaluate efficacy of pharmacologic agents. A recent systematic review of the literature indicates that anticholinergic agents have superiority over placebo (RR 1.39, 95% CI 1.28 to 1.51). This means that while the effect is statistically significant it is just slightly over 1 [11]. On the other hand, the long–term effect of anticholinergic agents compared to placebo is equal. Furthermore, about 80% of patients with an over active bladder who receive anticholinergic and antimuscarinic agents stop taking drugs due to side effects (i.e., dry mouth, blurred vision, constipation, somnolence, dizziness, cognitive impairment and GE reflux) and Anticholinergic adverse events are much more frequent in elderly patients [12,13]. Side effects are also associated with alpha blockers and include asthenia, dizziness and Hypotension. Anticholinergics and selective alpha blockers have positive effects on urinary symptoms and pain but these drugs don't improve sexual life of patients [6-9].

There is a need for new alternatives for the treatment of lower urinary tract symptoms in this patients. Several epidemiological studies indicate the relationship between Lower Urinary Tract

Symptoms (LUTS) and ED (Erectile Dysfunction). This association is more than a coincidence and in fact has a causal relationship [14]. Multiple studies described Lower Urinary Tract Symptoms alleviation in patients who were treated for ED with PDE5 inhibitors [15,16]. Tadalafil is one of these therapeutic options that widely applied in treating ED. The half-life of Tadalafil is 17.5 hours; it attains steady state concentrations with once daily dosing during 5 days [17,18]. Kevin et al. demonstrated that Tadalafil was well tolerated with once daily administration. They detected clinically and statistically significant improvement in lower urinary tract symptoms/benign prostatic hyperplasia [19]. Tadalafil is being investigated for the treatment of LUTS suggestive of benign prostatic hyperplasia (BPH-LUTS). The majority of stent patients is young and had active sexual relations, impact on sexual life is very important. Given that this study is designed to evaluate the effects of Tadalafil on alleviation of lower urinary tract symptoms, pain, general health, sexual life and work status of patients with ureteral stents based on Ureteral Stents Symptom Questionnaire.

2. MATERIALS AND METHODS

2.1 Setting and Design

This trial is a single center, parallel-design, randomized, controlled and triples blind study. This clinical study was conducted at Imam Reza teaching hospital and the Urology Department of Tabriz University of Medical Sciences in Iran. Subject recruitment began in December 2013. Male patients with unilateral ureteral stent were enrolled to this trial. Participants randomized 1: 1 into A or B groups. For 28 days, all patients were treated with placebo or Tadalafil 10 mg daily [19,20,21,22]. Data was collected before and immediately after the 28 day treatment period.

The study design scheme is illustrated in Fig. 1 and describe in detail below according to the CONSORT 2010 statement.

2.2 Subject Inclusion and Exclusion

Fifteen to seventy years old male patients, who had indication for unilateral ureteral stent (DJ), were enrolled to the study. The planned recruitment period was three months, but due to academic travel of our team endourologist, recruitment time was longer than predicted. Patients with history of hypertension, heart or respiratory disease, stroke, hypotension, renal or liver failure, retinitis pigmentosa, severe headache, consumption of nitrate drugs and a positive urine culture, or who had any allergic reaction to Tadalafil were excluded from this trial. During the course of the study, subjects excluded if 1) major side effect was seen (e.g., severe hypotension, severe headache); 2) subject misses a significant number of treatments; 3) reliable data cannot be obtained; or 4) subjects desire to discontinue treatment.

2.3 Sample Size

As the required data for sample size calculation of the current study was not available, after pilot study and data collection, sample size was calculated based on superiority hypothesis with Clinical importance margin of 25% Standard Effect Size (Table 1). According to Table 1 data, ideal sample size was estimated 108 (54 patients for each Intervention and control group). Sample size was calculated by STATA version 11 statistical software package.

2.4 Recruitment and Consent

All participants were informed of the trial at the surgical admission. All participants were asked and examined for eligibility criteria, and if appropriate, were enrolled in the trial. Prepared Written informed consent was submitted to volunteers by a member of the research team at the first.

2.5 Randomization Procedure and Blinding

Randomization carried out using a computer based randomization protocol by an epidemiologist independent of the study. STATA software were used to perform a block randomization, generating a sequence of 108 random numbers in 1:1 allocation between the two groups. Random allocation will be done by central call system. Placebo tablets were made from starch by pharmacy faculty of Tabriz University of Medical Sciences at the same shape, size and color of Tadalafil. Tadalafil and placebo will be packed in similar packages and encoded as A and B. None of the physicians, nurses, patients, neither the outcome assessor nor the statistical analyzers are aware of designated intervention. Blinding will be maintained after outcome assessment.

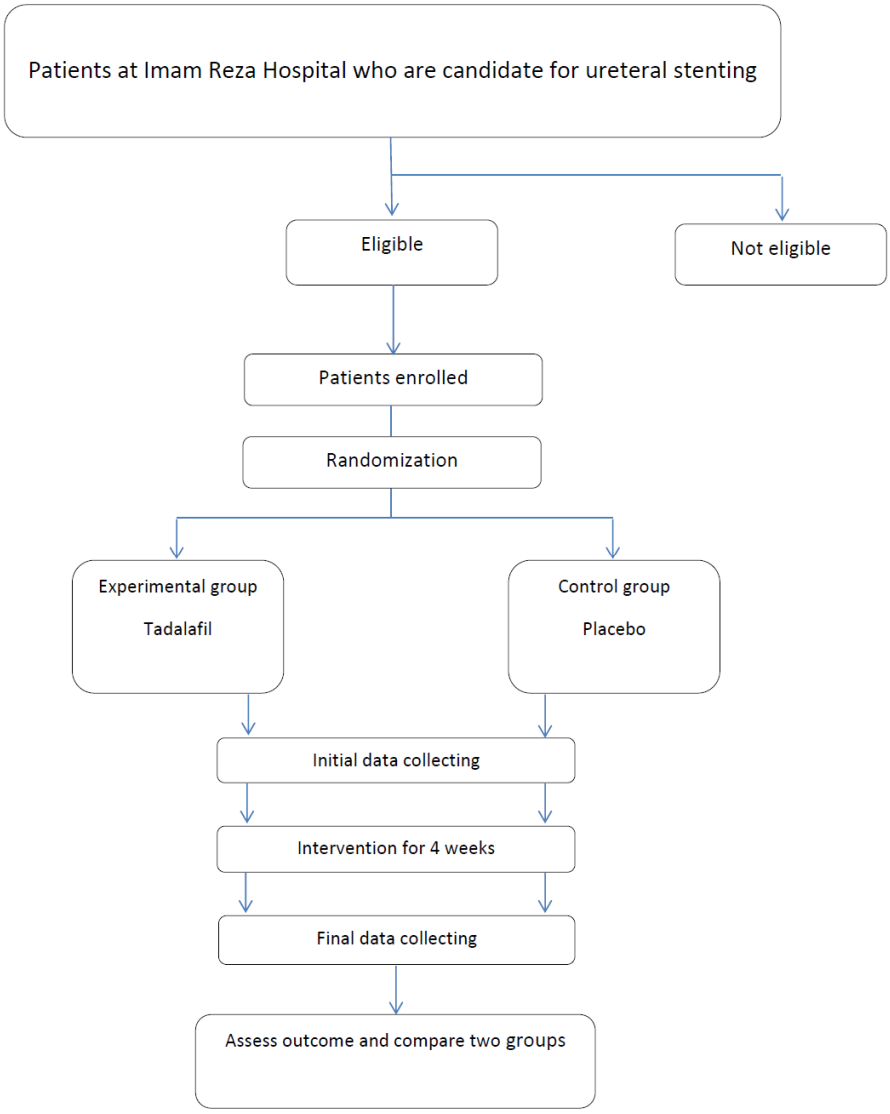

Fig. 1. Study design scheme

Table 1. Calculated sample size for 3 domains

Domain	Mean difference	Hypothesis type	Standard effect size (SES)	Clinical importance margin	Type I error	Type II error	Sample size
Urinary symptoms	2.89	Equality (one sided)	2.35	-	0.05	0.2	70(35*2)
Urinary symptoms	2.89	Superiority	2.35	0.59 (25% SES)	0.05	0.2	108(54*2)
Body pain	4.8	Superiority	3.05	2.29 (75% SES)	0.05	0.1	40(20*2)
Sexual matter	2.7	Superiority	2.96	0.74 (25% SES)	0.05	0.1	64(32*2)
Sexual matter	2.7	Superiority	2.96	0.74 (25% SES)	0.05	0.2	46(23*2)

2.6 Ethics

This trial has been approved by Tabriz University of Medical Sciences' local ethics committee (9291) and was registered at the Iranian Clinical Trial Registry (IRCT2013113015597N1). All aspects of the study are conducted with adherence to the current version of the Declaration of Helsinki. Written informed consent was required of all study participants.

2.7 Intervention

Each control group participant receives placebo tablets once per day by oral route. Each patient in the experimental group receives Tadalafil tablets once daily (10 mg per tablet, Chemidarou Pharmaceutical Co). All of patients (both groups' members) take prophylactic antibiotics as our department routine policy. Every participant enrolled in the trial, as mentioned earlier, receives medications (Placebo or Tadalafil) for 28 consecutive days.

2.8 Primary Outcomes

The Ureteral Stent Symptom Questionnaire (USSQ) was selected as the primary outcome assessment. It has been developed for ureteral stent symptom and quality of life evaluation. Urinary symptoms (i.e., urgency, frequency, nocturia, dysuria, hematuria and incomplete emptying), pain (i.e., abdominal, flank, inguinal, genital severity of pain, association with physical activity, rest and voiding), General health, sexual matters and work performance in patients with ureteral stents will be assessed. Scores for subscales and a global score will be compared by groups (control or experimental). The validation of the Ureteral Stent Symptom Questionnaire was done by the authors and reported in 16th Annual IUA (Iranian Urology Association) Congress 14th – 17th May 2013 [23].

2.9 Secondary Outcomes

Secondary outcomes considered are cardiovascular, respiratory, gastrointestinal, neurologic, and musculoskeletal side effects and are recorded in both groups.

2.10 Data Collection

At recruitment, before treatment for the trial is initiated, each patient's full medical history was recorded, along with vital signs and all current medications. Laboratory tests were include blood urea nitrogen, Creatinine, urine analysis and urine culture. At the end of the intervention phase (four weeks) self-assessment Ureteral Stent Symptom Questionnaire will be administrated.

2.11 Statistical Analysis

Data will be analyzed using STATA version 11 statistical software package. The change in global score of USSQ and in each section will be compared between two groups using either parametric or nonparametric tests considering the distribution of the data. Relative Risk (RR), Number Needed to Treat (NNT) and Risk Difference (RD), along with their 95% confidence intervals will be calculated for appropriately dichotomized endpoints. The principal analysis will be on an intention to treat basis. A p-value below 0.05 will be considered as significant when interpreting the statistical tests.

3. TRIAL STATUS

Recruitment to this trial commenced in December 2013 and is on-going at the time of manuscript submission. The expected time of recruitment completion is June 2014.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties).

ETHICAL APPROVAL

This project is approved by Tabriz University of Medical Sciences ethical committee with 9291 number. Scanned copy of the Ethical Committee Approval submitted you.

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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