MODERATED POSTER

Sildenafil citrate for Erectile Dysfunction in Patients with End Stage Renal Disease

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Objective: To assess the available literature evaluating the safety and efficacy of sildenafil citrate in improving erectile function in patients with end stage renal disease

Methods: From the period of 1990 - June 2016, the authors assessed the Cochrane Register of Controlled Trials and Medline for randomized controlled trials evaluating the safety and efficacy of sildenafil citrate for the treatment of erectile dysfunction in patients with chronic renal disease. Review authors selected articles for inclusion, extracted data and assessed trial quality. Risk ratios were determined and reported for dichotomous data and mean differences with 95% confidence intervals for continuous data.

Results: Three randomized control trials involving a total of were identified. All trials investigated the safety and efficacy of sildenafil citrate in patients with chronic renal disease. Pooled analysis of the trials showed statistically significant improvement in the IIEF score with sildenafil citrate on the study as well as on the meta-analysis level. Pooled analysis of all three trials shows no statistical difference with regards to side effects between the treatment arms on the meta-analysis level. Common side effects include nausea, headache and palpitation.

Conclusion: Based on the meta-analysis of the available literature, oral sildenafil citrate is an effective and safe treatment for erectile dysfunction in patients with chronic kidney disease.

Key words: sildenafil citrate, erectile dysfunction

Introduction

Erectile dysfunction is the inability to achieve or maintain an erection for a satisfactory sexual perforamance.[1] Erectile dysfunction in end stage renal disease patients is often due to the alterations in the hypothalamic-pituitary-gonadal axis, autonomic neuropathy and derangements in the arterial supply or venous outflow in the cavernous body.[2]

Current literature shows that ED is present in at least 70%-80% of patients in this population.[3] It is one of the factors negatively influencing the quality of life in patients with end stage renal failure. The resulting stress of ED often impacts interaction with others especially the sexual partner.[4] In spite of regular dialysis, ED often progresses and worsens with time.

Sildenafil citrate is the first oral and most widely prescribed treatment for ED. It acts by inhibiting phosphodiesterase type 5 (PDE5), an enzyme that promotes degradation of cGMP (cyclic guanosine monophosphate) in the corpus cavernosum. The presence of cGMP promotes increase blood flow into the penis thereby promoting erection.[5] It is considered an effective and well-tolerated drug in the treatment of male

ED in the general population. However, there have only been a few studies on the use of sildenafil citrate in chronic renal failure patients and have not been subjected to a systematic review. This systematic review aimed to determine the safety and efficacy of sildenafil citrate for the treatment of erectile dysfunction in patients with end stage renal disease from the current available literature.

The main objective of this review was to assess the available literature evaluating the safety and efficacy of sildenafil citrate in improving erectile function in patients with end stage renal disease.

Materials and Methods

Search for Identification of Studies

The following databases were used to identify studies for this systematic review (Pubmed 1990 to June 2016 and Cochrane 1990 to date of issue). The search terms used were "hemodialyis, erectile dysfunction and sildenafil". The reference lists of relevant articles were also searched. Date of the search was June 2016.

Type of Participants

Patients included in the study were those with end stage renal disease and on chronic dialysis (HD) with erectile dysfunction.

Types of Intervention

One arm involved patients with end stage renal disease and erectile dysfunction who were given sildenafil citrate (50-100 mg) at a specific time interval. The other arm involved patients who were given placebo.

Types of Outcomes

The primary outcome of interest was the improvement in IIEF score following intake of sildenafil citrate versus placebo. The authors also took into consideration the adverse events of sildenafil citrate versus placebo in patients with end stage renal disease.

Types of Studies/Methodologies and Process of Selection

Study design criteria for inclusion in this review were randomized controlled trials (RCT), in any language but preferably in English with any level of blinding and containing any number of individuals of whom at least 80% were followed up.

Study Appraisal / Assessment of the Risk of Bias

The risk of bias in eligible trials was assessed independently by two reviewers using the Cochrane risk of bias tool. The following factors were considered: the presence of adequate random sequence generation and allocation concealment, proper blinding, and freedom from selective reporting.

Data Collection and Analysis

The titles and abstracts of all studies identified by the search strategy were assessed independently for possible inclusion by two reviewers. The full texts of all potentially relevant studies were retrieved and assessed for final inclusion into the review based on the preset criteria. Standardized data extraction forms were used independently by two reviewers and cross-checked.

Measures of Treatment Effect

The following comparison was made:

1. Treatment of erectile dysfunction for patients with end stage renal disease with sildenafil citrate versus placebo

The outcomes studied in this review included the following:

1. Improvement in the IIEF score of patients
2. Number of patients who had adverse events

Data Synthesis

Included data have been processed as described in the Cochrane Handbook. Risk ratios were

determined and reported for dichotomous data and mean differences with 95% confidence intervals for continuous data. A fixed effect model was used in data analysis.

Results

Records identified through database and manual searching last June 2016 showed an initial retrieval of 46 results. After screening for duplicates and unclear articles, a total of 10 full text articles were assessed for eligibility. Two were excluded due to non-relevant participants (peritoneal dialysis and post transplant patients), 2 with non-relevant interventions (sildenafil versus vardenafil) and 3 were eliminated due to being a non-RCT.

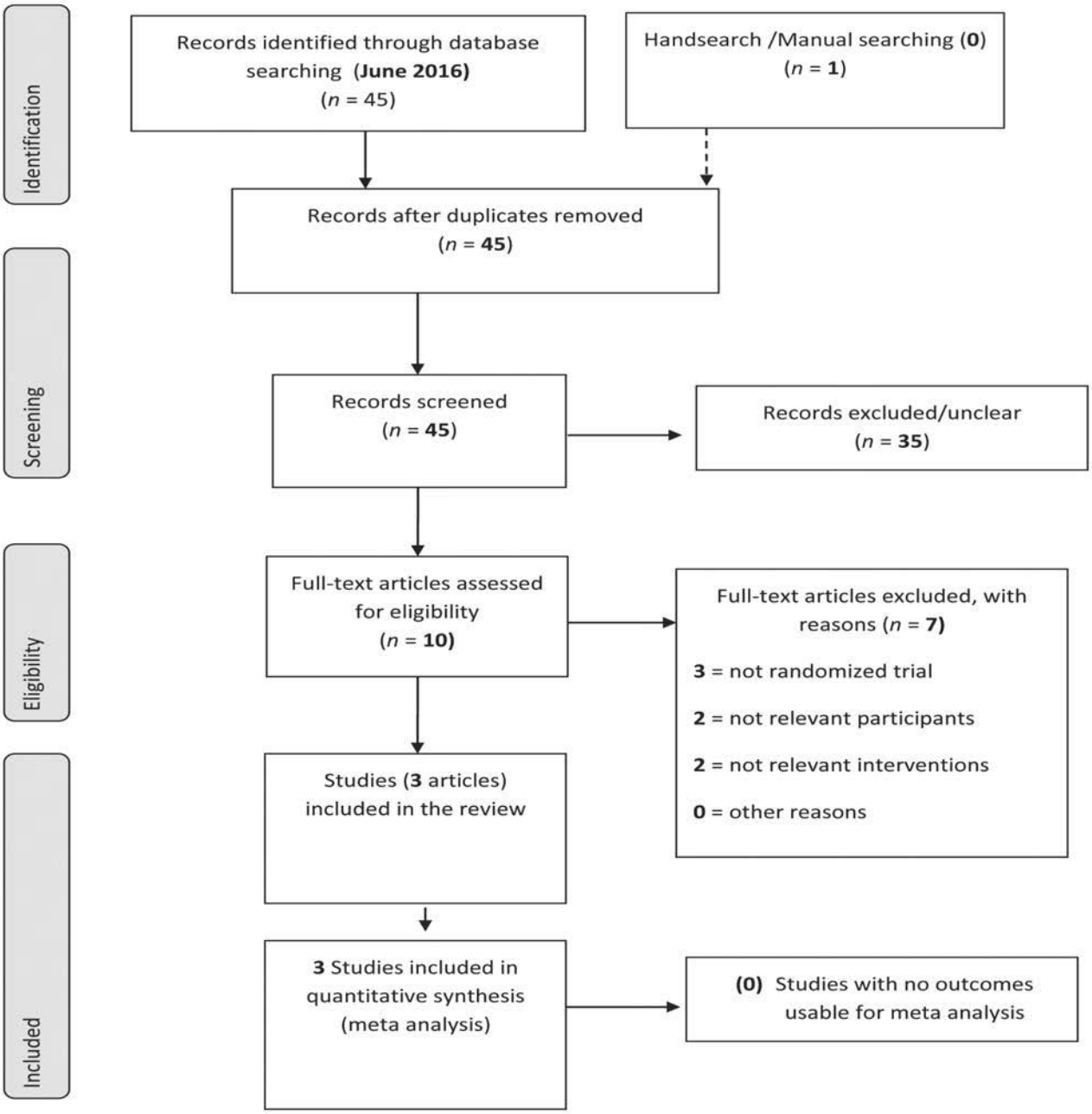

Figure 1. PRISMA flow diagram

Description of Included Studies

Three studies for a total of 118 patients comprised the evidence for this review. Two studies were done in 2010 and the third one was done in 2002.

Patient population in the three studies included adult patients with end stage renal disease with erectile dysfunction. Patients included in the study should have undergone hemodialysis for at least 6 months, had a stable female sexual partner for at least 1 year and have no history of diabetes, previous myocardial infarction/stroke, cirrhosis and penile anatomic abnormalities. Erectile dysfunction (ED) was defined in all three studies as having a score of 25 or less in the IIEF erectile domain function score.

In all three studies, patients were then randomized into two groups: one group was enrolled in the sildenafil group (experimental) and the other group in the placebo (control).

Primary outcome of this review was to evaluate the efficacy and safety of sildenafil citrate in treating erectile dysfunction in ESRD patients. Efficacy was defined as the improvement in the IIEF score one week after intake of sildenafil citrate. An adverse event was defined as any untoward incident during the trial period, which altered the clinical course of the patient. This included nausea, headache, palpitation, flushing and chest pain.

Allocation to one of the two arms was obtained from a generated randomization list in all three studies. In all three studies, concealment was done by repackaging sildenafil citrate and placebo in identical capsules and placed in sealed boxes before giving to patients. They were instructed to take the capsules on non-dialysis days and one hour prior to sexual intercourse. All the three studies were double blinded. None of the authors or patients had access to the drug codes until patient evaluations were finished.

All the enrollees in the three trials were successfully followed up. In the study by Seibel, two patients withdrew due to personal reasons. In the study by Sallami, one patient discontinued sildenafil because on intense headache.

The efficacy of sildenafil versus placebo was assessed by re-administering the IIEF questionnaire after one week of therapy. The difference in their IIEF scores after treatment with either placebo or sildenafil was then pooled for statistical analysis.

There were two mortalities noted in the study of Seibel. Neither death was associated with drug ingestion or sexual intercourse.

Improvement in the Internal Index of Erectile Function (IIEF) Score

Pooled analysis of two trials showed statistically significant improvement in the IIEF score with sildenafil citrate on the study as well as on the meta-analysis level.

Side Effects

On the study level, side effects are lower on the control group as compared to the experimental (sildenafil). However, pooled analysis of all three trials shows no statistical difference with regards to side effects between the treatment arms on the meta-analysis level.

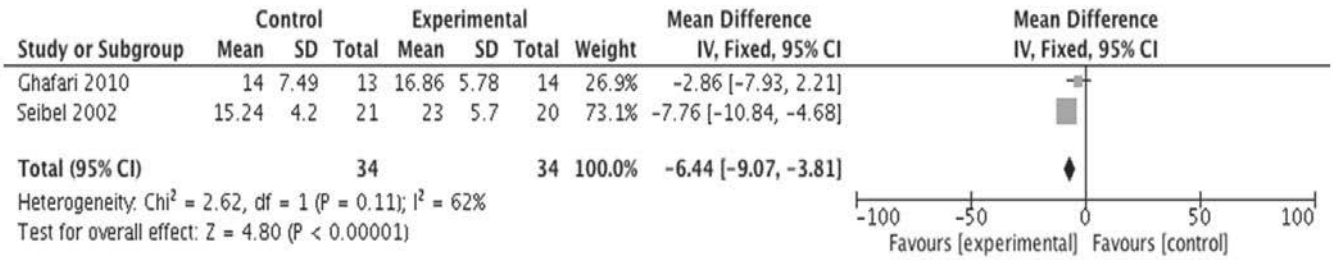

Figure 1. Meta-analysis of studies comparing improvement in IIEF score between placebo (control) and sildenafil citrate (experimental).

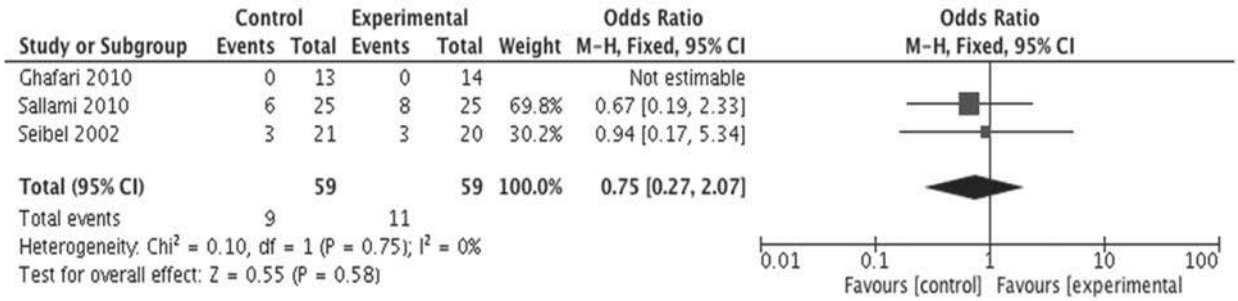

Figure 2. Meta-analysis of studies comparing adverse events between sildenafil citrate (experimental) and placebo (control).

Discussion

The primary objective of this review was to show the safety and efficacy of sildenafil in treating erectile dysfunction in chronic kidney disease patients. There have been few studies on the use of sildenafil in patients with chronic kidney disease. Majority of the literature involved open label prospective studies only. Prospective studies identified for this review have shown that sildenafil citrate is effective and safe in the treatment of chronic kidney disease patients. Chenk, et al. (2000) treated 34 patients with 50 mg sildenafil for 6 months and noted to be effective in 80% of the patients.[8] Yenicerioglu in 2002, reported that 20 of 30 hemodialysis patients had improved erectile function with sildenafil citrate.[7] Sahin in 2004 also reported that 38 of 51 patients had improved IIEF scores following an open label study with sildenafil.[8] With regards to its safety, all the open label prospective studies showed that sildenafil citrate was well-tolerated in the population of chronic kidney disease patients. There were few reported side effects, only headache and palpitation.[6,7,8]

In this systematic review, there were 3 randomized control trials identified. All of them had the same population of patients with chronic kidney disease. In all three studies, erectile dysfunction was identified by having patients answer a preliminary IIEF questionnaire. Patients with a score of less than 26 were included for the study. All three RCT's gave an initial dose of 50 mg sildenafil citrate versus placebo. With regards to the improvement of IIEF scores, only two studies (Seibel and Ghafari) showed the actual breakdown of the IIEF scores before and after treatment. These 2 studies were the only ones included in the final meta analysis. The study done by Sallami in 2010 only indicated the number of patients who improved after treatment. Results only showed that 19 out of the 25 patients in the sildenafil group had improved erectile function scores as compared to only 3 of 25 patients in the placebo group. In the sildenafil group, 5 patients noticed improvement with the use of 50 mg whereas 14 patients had to use 100 mg of sildenafil for erectile function improvement. Mean and standard deviation of the IIEF score were not indicated in the study. The study by Seibel in 2002 showed that sildenafil citrate was superior to placebo in treating erectile dysfunction in the chronic kidney disease population. There was an improvement in the erectile function in 85% in the sildenafil group as compared to only 9.5% in the placebo. There was also note of a mean 7-point improvement in the IIEF score for patients in the sildenafil group. The study by Ghafari in 2010 also demonstrated a 5 point improvement in the IIEF score in the sildenafil group. From pooled analysis of the present review of the two selected RCT's, sildenafil citrate was effective in treating erectile dysfunction in patients with chronic kidney disease. Pooled analysis of two trials showed statistically significant improvement in the IIEF score with sildenafil citrate on the study as well as on the meta-analysis level.

In all the studies reviewed, the use of sildenafil citrate in this population appears to be safe and the side effects are minor and well-tolerated. Majority of these include nausea, palpitation and headaches. In the study by Ghafari in 2010, no

side effect was reported in the 14 patients in the sildenafil group. In the study by Seibel in 2002, three patients had minor side effects of flushing, headache and dyspepsia. Analysis of their data showed that in terms of side effects, the results favor the placebo group in the study level. However pooled analyses of the three RCT's showed that were was no statistically difference between the two groups in the meta-analysis.

Conclusion

Oral sildenafil citrate is an effective and safe treatment for erectile dysfunction in patients with chronic kidney disease.

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