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Original Article

The clinical efficacy and safety of sildenafil in premature ejaculate: a meta-analysis

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Abstract: This study aims to assess the efficacy and safety of sildenafil therapy compared with other agents in patients with premature ejaculation (PE) but without erectile dysfunction (ED). Systematically literature search was performed using PubMed, EMBASE, Medline, Science Direct/Elsevier, CNKI, and the Cochrane Library. The mean difference (MD) or relative risk (RR) and 95% confidence intervals (CI) were used to assess the efficacy and safety of sildenafil treatment compared with other agents in men with PE. 13 studies, including 506 cases and 506 controls, were identified. The results suggested that when compared with other agents, sildenafil had a better effect on intravaginal ejaculation latency time (IELT) (MD: 1.56, 95% CI: 1.23-1.90), number of coitus per week (MD: 0.78, 95% CI: 0.72-0.84) and overall coitus satisfaction rate (RR: 1.32, 95% CI: 1.17-1.48), However, a higher but acceptable rate of adverse events was found in the patients treated with sildenafil (RR: 2.13, 95% CI: 1.28-3.53). The present study shows that sildenafil was more effective in prolonging IELT, increasing the number of coitus per week and increasing the overall coitus satisfaction rate with an acceptable rate of side effects than other treatment agents.

Keywords: Intravaginal ejaculation latency time, premature ejaculation, sildenafil, meta-analysis, relative risk

Introduction

PE is defined as persistent ejaculation with minimal sexual stimulation before or soon after penetration, in which the individual has minimal voluntary control over [1]. PE has become one of the most common diseases in urology and estimated prevalence is more than 21%, and perhaps 75% of men at some point in their lives are affected [1, 2]. Quality of life and social interaction in men with PE suffered a serious impact, as well as low satisfaction with sexual intercourse [3-5].

At present, psychotherapy and behavior training therapy have poor patient adherence rates with PE [6, 7]. Pharmaceutical therapy is still recommended as the first priority for the consistent treatment of PE [8]. Agents such as selective serum reuptake inhibitor substances (SSRIs), local anesthetics and phosphodiesterase type 5 (PDE5) inhibitors have been developed specifically for the treatment of PE and are widely used in many countries. 13 studies have investigated the therapeutic role of sildenafil in PE [9-21]. However, the use of sildenafil in the treatment of PE requires further investigation because these results were inconsistent. Hence, in this study, we conducted a meta-analysis through searching studies from PubMed, Medline and CNKI to assess the efficacy and safety of sildenafil treatment compared with other agents in men with PE.

Material and method

Literature search

The study search strategy was conducted according to the handbook of the Cochrane collaboration, and an electronic searching was performed using PubMed, EMBASE, Medline, Science Direct/Elsevier, CNKI, and the Cochrane Library. The studies of these databases were published between January 1980 and March 2016. The following keywords (both alone and in combination) were used in the search: “premature ejaculation”, “sildenafil” and “PDE5 inhibitors”.

Inclusion criteria

All of the studies included in the meta-analysis met the following criteria: 1. The study had a

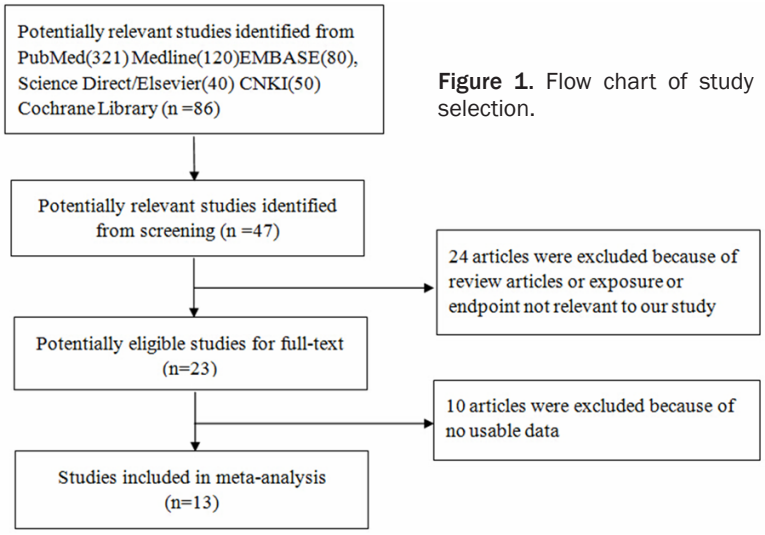

Figure 1. Flow chart of study selection.

case-control or RCT study design; 2. Patients in the studies were aged more than 18 years, with a history of lifelong PE but without ED, who met the PE definition of international society for sexual medicine (ISSM) or Diagnostic and Statistical Manual of Mental Disorders (DSW-IV), and had a stable, monogamous, heterosexual relationship with a duration was more than 6 months; 3. The study compared the efficacy and safety of two therapeutic methods (sildenafil and other agents); 4. The study had available data that could be extracted from the article or obtained by calculation.

Study selection

The literatures searched from data base were screened by two independent reviewers. When the relevancy of the study was uncertain, a subsequent full-text assessment was conducted. Review articles, case reports, comments, meeting abstracts and editorials were excluded. Because the data included in this study were retrieved from the literature, ethical approval from an ethics committees was not needed.

Data extraction and quality assessments

The extraction data included the following: the last name of the first author, publication year, study population, mean ages of participants, study design features, number of cases and controls, study interventions and the efficacy and safety outcomes.

Based on the standard criteria (randomization, blinding, and failure to follow-up and using the scoring system developed by Jadad et al. [22], the quality of included studies was evaluated.

Statistical analysis

A meta-analysis was used to pool the efficacy results and was conducted using Review Manager 5.1 and STATA 5.0 software. Based on a random-effects model or, in the absence of heterogeneity, a fixed-effects model, the MDs or RRs and the corresponding 95% CIs were used to measure the efficacy and safety of sildenafil treatment compared with other agents in men with PE. Homogeneity tests were performed with the use of Q statistic and the I^2 statistic. When the *P* value was less than 0.05, it was considered statistically significant.

Results

Study selection process and study characteristics

Figure 1 presents a flow chart showing the study selection process. Initially, we identified potential studies from PubMed, EMBASE, Medline, Science Direct/Elsevier, CNKI, and the Cochrane Library. After screening the abstracts or titles, most of them were excluded because they were letters and reviews or the exposure and endpoint were not linked to our study. After that, 13 studies [9-21], including 506 cases and 506 controls, were identified.

Table 1 depicts the study characteristics of the included studies. They were published from 2002 to 2014. Of these studies, eight were conducted in the Chinese population [10, 11, 15, 17-21]. The remaining five studies were conducted in the Italian, Australian, Turkish, Iranian and Egyptian populations. The endpoints of our study included intravaginal ejaculation latency time, number of coitus per week, overall coitus satisfaction rate and adverse events.

Table 1. The characteristics of the included studies

Study (Year)	Population	Sample Size (n) case/control	Rang of age	Treatment case/control	Endpoints	Quality grade
Salonia et al. (2002)	Italian	40/40	19-47	Sildenafil + paroxetine/paroxetine	IELT, numbers of coitus per week, adverse events	2
Tang et al. (2004)	Chinese	30/30	29-46	Sildenafil + behavior/behavior	IELT, numbers of coitus per week, adverse events	2
Zhang et al. (2005)	Chinese	36/36	18-42	Sildenafil + sertralin/sertralin	IELT, numbers of coitus per week, adverse events, coitus satisfaction rate	2
McMahon et al. (2005)	Australian	73/71	18-65	Sildenafil/placebo	IELT, adverse events	3
Atan et al. (2006)	Turkish	20/20	20-52	Sildenafil/placebo	Adverse events, coitus satisfaction rate	2
Li et al. (2006)	Chinese	35/35	N	Sildenafil + seroxat/seroxat	IELT, numbers of coitus per week, coitus satisfaction rate	2
Li et al. (2007)	Chinese	34/34	18-52	Trazodone hydrochloride + sildenafil + behavior/trazodone hydrochloride + behavior	IELT, coitus satisfaction rate	2
Hou et al. (2008)	Chinese	30/30	25-50	Sildenafil + sertralin/sertraline	IELT	2
Hosseini et al. (2007)	Iranian	43/48	21-43	Sildenafil/fluoxetine	Adverse events, coitus satisfaction rate	2
Wang et al. (2007)	Chinese	60/60	--	Sildenafil/paroxetine	IELT, numbers of coitus per week, adverse events	2
Jiang et al. (2011)	Chinese	40/40	21-47	Sildenafil + lidocaine/lidocaine	Coitus satisfaction rate	2
Gameel et al. (2013)	Egyptian	30/27	26-39	Sildenafil/placebo	IELT	3
Wu et al. (2014)	Chinese	35/35	N	Silaenafil + psychological behavior/psychological behavior	IELT	2

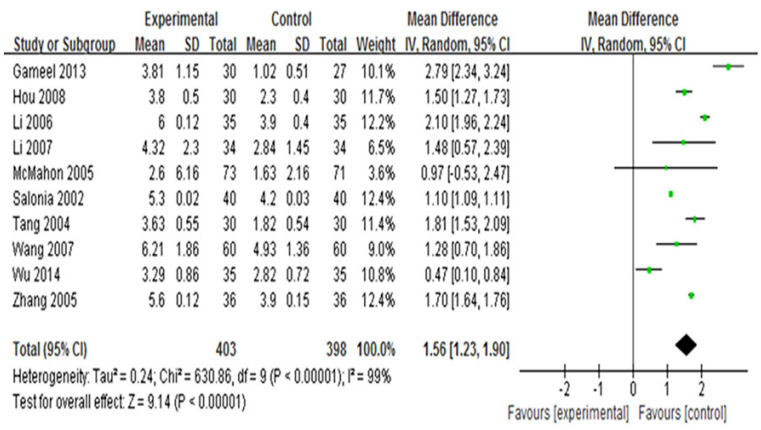

Figure 2. The IELT comparison between sildenafil and other agents.

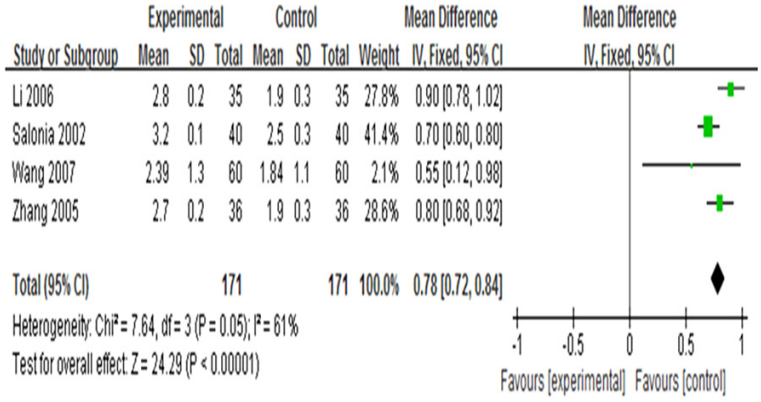

Figure 3. The number of coitus per week comparison between sildenafil and other agents.

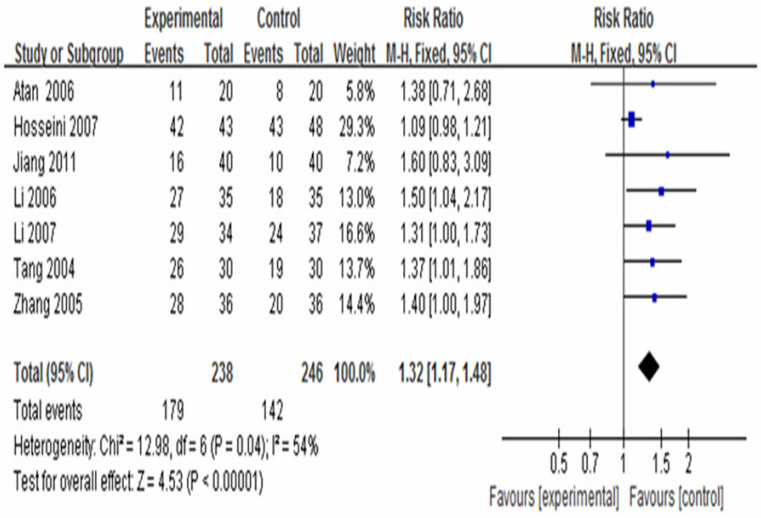

Figure 4. The coitus satisfaction rate comparison between sildenafil and other agents.

Meta-analysis results

Intravaginal ejaculation latency time (IELT): Ten studies reported the differences in IELT between sildenafil and other treatment agents. Of these studies, only one study showed there was no difference [12], and the other five studies found a significant difference. The pooled results showed that there was a significant difference in IELT between the two therapeutic methods (MD: 1.56, 95% CI: 1.23-1.90), however, a strong evidence of heterogeneity among these studies was found (I^2=99%, P<0.05). The results are presented in **Figure 2**.

Number of coitus per week: Four studies were included to assess whether there was any difference in the number of coitus per week between these two therapeutic methods, and all of them showed an increase in the number of coitus per week after treatment with sildenafil. Pooled analysis showed that the number of coitus per week in the patients with sildenafil treatment was higher than that in the men treated with other agents (MD: 0.78, 95% CI: 0.72-0.84). Little evidence of heterogeneity was found (I^2=61%, P=0.05). The results are presented in **Figure 3**.

Overall coitus satisfaction rate: Seven studies reported coitus satisfaction rate at the end of treatment. Compared with other agents, sildenafil treatment significantly increased the coitus satisfaction rate, the RR (95% CI) was 1.32 (1.17-1.48). The results are shown in **Figure 4**.

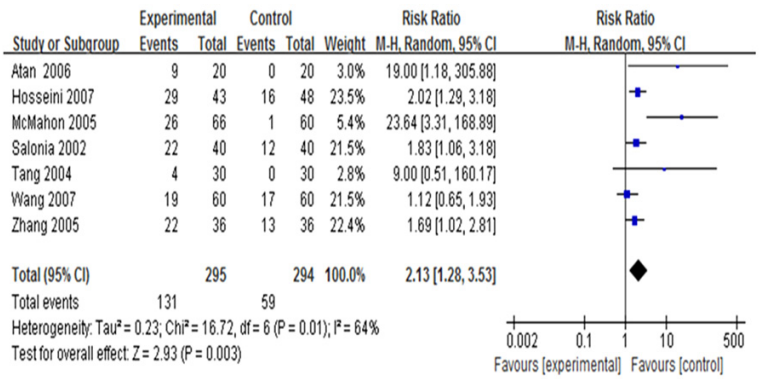

Figure 5. The adverse events comparison between sildenafil and other agents.

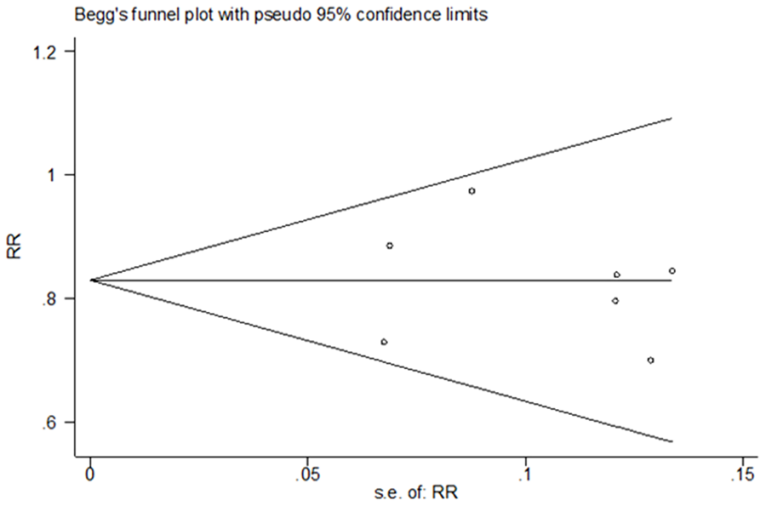

Figure 6. Funnel plot of publication bias.

Adverse events: All included studies presented the adverse events data. The most common adverse events included headache, flushing, dyspepsia, abnormal vision and nausea. Based on a random-effects model, compared with other agents, sildenafil had a higher adverse reaction rate, the combined RR (95% CI was 2.13 (1.28-3.53). **Figure 5** presents the results of the adverse events comparison between sildenafil and other agents.

Publication bias: The adverse reaction rate was assessed for publication bias. Begg's test and Egg's test showed low evidence of publication bias found among the included studies using STATA 12.0 (P=0.897). The results of the publication bias assessment is presented in **Figure 6**.

Discussion

In this study, we assessed the efficacy and safety of sildenafil treatment compared with other agents in patients with PE but without ED. We found that there was a longer IELT, higher frequencies of coitus per week, and a higher overall coitus satisfaction rate from the patients with sildenafil treatment than the patients with other treatments. Although sildenafil treatment had a higher adverse reaction rate, all of the side effects were acceptable, including headache, flushing, dyspepsia, abnormal vision and nausea. No severe complications were observed.In the early studies, it was postulated that psychological and physiological factors or the combined action of these two factors might be the dominant causes of PE [23]. With a deepening of the understanding of PE, several studies suggested that the prostate urethra-ball sponge reflection and the excitability, the sensitivity of the posterior urethral pressure change, and many factors influencing the posterior urethral pressure changes of the nervous system played important roles in the ejaculation process [24]. Lately, neuroendocrine factors have gradually become the focus of studies on PE etiology.

The therapeutic methods of PE are varied, including the replacement of previously administered psychosexual cognitive behavioral therapy with an integrated treatment approach, topical agents, SSRIs, PDE5 inhibitors and acupuncture [8]. Behavioral therapy has been shown to be minimally effective because the results are not durable and patients have low compliance [24]. Several topical therapies have also been used, including severance-secret cream, lignocaine spray, lidocaine-prilocaine cream and lidocaine-prilocaine spray. The most prominent side effects are penile numbness

and local symptoms of irritation, burning, and delayed ejaculation [6]. However, these topical therapies have lower coitus satisfaction rates for patients and their partners.

Recently, several studies have reported that PDE5 inhibitors, as a first line oral pharmacotherapy for ED, have efficacy for alleviating PE [26]. Sildenafil, a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5, has typically been chosen to treat patients with PE [27]. Some studies have evaluated the efficacy and safety of sildenafil for the management of PE. 13 studies were retrieved for this review after searching online databases. These studies met quality criteria regarding patient selection, outcome measurement specification, and appropriateness of follow-up. However, the effect of this drug in these studies was controversial; it may be associated with the existence of several methodological flaws which significantly affected the results of our study. Most importantly, the absence of widely accepted and unique definitions created a bias for the investigation of the sildenafil treatment outcomes. In this study, we found that sildenafil was more effective than other treatments in prolonging IELT, increasing the number of coitus per week and increasing the overall coitus satisfaction rate, with acceptable side effects.

The mechanisms of sildenafil in the treatment of PE are unclear. However, the potential mechanisms are related to the NO-cGMP pathway. Cyclic guanosine monophosphate (cGMP) is generated by cytoplasmic soluble guanylatecyclases, and the phosphodiesterase type 5 (PDE5) enzyme is highly specific for hydrolysis of cGMP. First, sildenafil, a PDE5 inhibitor, alleviates sympathetic tone and inhibits smooth muscle dilation of the vas deferens and seminal vesicles to delay ejaculation through increasing NO generation [28]. Second, sildenafil induces peripheral nerves to produce a status of alganesthesia, which helps to reduce the sensitivity of the penis in some patients with premature ejaculation [29]. Third, the latent period of ejaculation is affected by the duration of the erection. Sildenafil prolongs the duration of erection, and the longer the duration of erection, the longer the latent period of ejaculation [30, 31].

This study has some limitations that should be considered. First, in our review, all of the included studies did not report the results of long-term follow-ups. Hence, it was difficult to determine the long-term curative effects and adverse reactions to sildenafil. Second, there was no unified standard of diagnosis and treatment and no uniform standard for classifying the severity of PE. Third, this study included both RCTs and observation studies. The clinical evidence was influenced by the observation studies. Fourth, strong evidence of heterogeneity in some of our results was found. The patients of the included studies were from different locations, had different basic characteristics and were of different pathological types. Fifth, the sample size of our study was still small, and more well-design RCTs studies should address these issues.

Although there were many limitations, our study has some important significance. This study was the first meta-analysis to estimate the efficacy and safety of sildenafil treatment compared with other agents in patients with PE but without erectile dysfunction (ED). Although individual studies had insufficient statistical power, 8 eligible studies, including a large sample size, were included in our meta-analysis, which greatly enhanced the statistical power and provided more reliable results. However, the most important finding was that we found a longer IELT, higher frequencies of coitus per week and an increase in the overall coitus satisfaction rate from the patients with sildenafil treatment than the patients with other treatment agents, and no severe complications were observed. These results provide important clinical significance for the patients with PE.

Conclusions

Our study found that sildenafil was more effective compared with other treatments in prolonging of IELT, increasing the frequency of coitus per week, and increasing the overall coitus satisfaction rate with acceptable rates of side effects. More well-design RCTs with long-term follow-up studies are warranted.

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Disclosure of conflict of interest

None.

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