

Peer Review File

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Review Comments:

Comment 1: Please modify sentence. Repetitive- procedure. Line 59- Postoperative ED has been reported in 15%–18% of patients who undergo NSRP (5, 6). Nearly 15%–18% of patients who underwent NSRP complained of Postoperative ED.

Reply 1: Thank you for your careful review. I have edited this sentence as your suggestion. The comments were described as follows and the text which was changed was highlighted in BOLD.

Changes in the text: (Page 5, line 66-68)

Postoperative ED has been reported in 15%–18% of patients who undergo NSRP (5, 6). **It is a condition that can potentially take a toll on the patients' everyday life (4).**

Comment 2: Line 61- statement unclear-ED becomes unlikely to occur procedure

Reply 2: I apologized that the meaning of the sentence is not clearly communicated. We revised the sentence to clarify the meaning according to your suggestion. The comments were described as follows and the text which was changed was highlighted in BOLD.

Changes in the text: (Page 5, line 68-69)

Therefore, if postoperative ED is less likely to occur, more patients will decide to receive NSRP.

Comment 3: Line 68- Provide references to support the statement and elaborate in the discussion-Several errors were found in meta-analyses and systematic reviews that have been performed to assess the efficacy and adverse effects of PDE5-Is...

Reply 3: I totally agreed your suggestion. Although I explained errors of previous systematic reviews in discussion section, I should provide the references. The comments were described as follows and the text which was changed was highlighted in BOLD.

Changes in the text: (Page 5, line 77-78)

Several errors were found in meta-analyses and systematic reviews that have been performed to assess the efficacy and adverse effects of PDE5-Is **(17-19).**

References

17. Limoncin E, Gravina GL, Corona G, et al. Erectile function recovery in men treated with phosphodiesterase type 5 inhibitor administration after bilateral nerve-sparing radical prostatectomy: a systematic review of placebo-controlled randomized trials with trial sequential analysis 2017;5(5):863-72.
18. Cui Y, Liu X, Shi L, et al. Efficacy and safety of phosphodiesterase type 5 (PDE5) inhibitors in treating erectile dysfunction after bilateral nerve-sparing radical prostatectomy. *Andrology* 2016;48(1):20-8.
19. Wang X, Wang X, Liu T, et al. Systematic review and meta-analysis of the use of phosphodiesterase type 5 inhibitors for treatment of erectile dysfunction following bilateral nerve-sparing radical prostatectomy. *PloS one* 2014;9(3):e91327.

Comment 4: Discussion- Previous reports were conflicting with the use of PDE5-Is alone for penile rehabilitation. Please discuss.

Reply 4: I fully understand your opinion. Meta-analysis has a high level of evidence because analysis is performed according to a predetermined form on a specific subject. However, there is a limitation in that non-RCT studies were not included. There is a limitation in that the analysis we conducted also did not include the studies suggested and could not be analyzed. Therefore, I added some sentences to clarify this limitation according to your opinion as below. The comments were described as follows and the text which was changed was highlighted in BOLD.

Changes in the text: (Page 18, line 320-325)

In terms of the level of evidence, although meta-analysis is at a high level, studies other than RCTs were not included. In addition, although there have been some studies on different subjects of penile rehabilitation, only studies satisfying the criteria for meta-analysis were included in this meta-analysis. In order to overcome these limitations, it is thought that analysis including all studies related to penile rehabilitation is necessary through systemic review in the further study.

Comment 5: Line 211- Statement-Our meta-analysis and systematic review of the efficacy and safety of PDE5-Is demonstrated the feasibility of this treatment as penile rehabilitation after NSRP.- This is not new. This has been demonstrated previously. What is new from your meta-analysis. Do you prove or disprove established concepts?

Reply 5: I appreciated your careful review. In the age of evidence-based medicine, systematic review plays an important role in clinical decision making. In this situation, errors in the previous systematic reviews gave clinicians wrong information for decision making. These analyses were performed by entering the intention-to-treat population as the total number, and not the complete study population, or by entering the value of the score change as the value of the score. Additionally, there were cases in

which the total population value and standard deviation value were incorrectly entered into the study data. Moreover, a retrospective study was included in a previous meta-analysis. Although the research subject of previous studies was the same as that of our study, our systematic review analyzed the results of 14 studies compared to only 6 to 8 studies included in the former. In addition, the quality of the evidence of the outcome data was evaluated using the GRADE approach in this systematic review. Taken together, our analysis provides a more accurate and reliable basis for penile rehabilitation, including the latest findings.

I totally agreed your opinion of the result of this study may be not new. However, as previously explained, our analysis provides a more reliable and recent basis for the efficacy and safety of PDE5-Is. The comments were described as follows and the text which was changed was highlighted in BOLD.

Changes in the text: (Page 15, line 254-268)

In these previous reports, errors in the data entered could be found, which has led to problems regarding the methodological query. **In the age of evidence-based medicine, systematic review plays an important role in clinical decision making.(37) In this situation, errors in the previous systematic reviews gave clinicians wrong information for decision making.** These analyses were performed by entering the intention-to-treat population as the total number, and not the complete study population, or by entering the value of the score change as the value of the score. **Additionally, there were cases in which the total population value and standard deviation value were incorrectly entered into the study data. Moreover, a retrospective study was included in a previous meta-analysis. Although the research subject of previous studies was the same as that of our study, our systematic review analyzed the results of 14 studies compared to only 6 to 8 studies included in the former. In addition, the quality of the evidence of the outcome data was evaluated using the GRADE approach in this systematic review. Taken together, our analysis provides a more accurate and reliable basis for penile rehabilitation, including the latest findings.**

Comment 6: There are few reports showing synergistic effect of combination therapies for early recovery of erectile function after NSRP. Authors should include these studies as well for the benefit of clinical providers.

Reply 6: I agree with your opinion and that is very good and delicate suggestion. It is true that what you pointed out is important, but since this study is a meta-analysis, the papers included in the analysis are bound to be limited to RCT compared the efficacy of PDE5-Is. The combination therapies for erectile dysfunction is important issue. Therefore, we added the sentence to reflect your opinion. The comments were described as follows and the text which was changed was highlighted in BOLD.

Changes in the text: (Page 17, line 296-302)

Nandipati et al. reported the effectiveness of combination therapy in penile rehabilitation and reported that combination therapy of intra-cavernosal injection and PDE5-I were effective for erectile dysfunction (44). According to reporting by Deng et al., the combination therapy of PDE5-I and vacuum erection device had a synergistic effect in penile rehabilitation (45). Although these studies were not included in this analysis because they did not meet the inclusion criteria, it should be considered that PDE5-I based combination therapy is effective in penile rehabilitation.

Comment 7: Authors should also comment on the impact of patient's age and comorbid conditions in PDE5-Is response rate in this population.

Reply 7: Thank you for your suggestion. A patient's age and comorbidities may be important factors that affect the PDE5-Is response rate. This is an important topic to be studied. Unfortunately, our study is a systematic review of previous published randomized controlled trials. Therefore, it was difficult to reveal the effect of the patient's age and comorbidities. Although we made every effort to the effect of each factor using subgroup analysis, only the regimen of PDE5-I treatment was available for subgroup analysis. I acknowledged that the inability to reveal the effect of the patient's age and comorbidities on the PDE5-Is response rate is a limitation of this study. This has been described in the limitation section and the text which was changed was highlighted in BOLD.

Changes in the text: (Page 18, line 315-319)

Third, a patient's age and comorbidities may be important factors that affect the PDE5-Is response rate. Although we made every effort to the effect of each factor using subgroup analysis, only the regimen of PDE5-I treatment was available for subgroup analysis. Further studies on the effect of the patient's age and comorbidities on the PDE5-Is response rate are needed.

Comment 8: Line 240- A subgroup analysis was conducted to assess the effects of the regimen of PDE5-I treatment, i.e., daily use and on-demand use.- Please provide this data in results.

Reply 8: I appreciated your suggestion. The detailed result of subgroup analysis should be described in the result section. I provided these data in the result section and the text which was changed was highlighted in BOLD.

Changes in the text:

(Page 12, line 181-185)

A subgroup analysis was conducted according to the regimen of PDE5-I treatment. The subgroup analysis revealed significantly improved IIEF domain scores for both daily use (MD = 4.68, 95% CI = 3.89 to 5.46, P < 0.00001, I² = 0%) and on-demand use (MD = 4.98, 95% CI = 3.57 to 6.39, P = 0.0003, I² = 74%).

(Page 12, line 189-192)

The subgroup analysis revealed that the incidence of these events was significantly higher for daily use (OR = 1.68, 95% CI = 1.15 to 2.45, P = 0.007, I² = 0%) and on-demand use of PDE5-Is (OR = 2.76, 95% CI = 1.34 to 5.69, P = 0.006, I² = 70%).

(Page 12, line 196-198)

The subgroup analysis revealed a significantly higher positive response rate for on-demand use of PDE5-Is (OR = 2.39, 95% CI = 1.81 to 3.15, P < 0.00001, I² = 34%).

(Page 12, line 200-203)

The subgroup analysis also revealed a higher positive response rate to SEP question 3 for daily use (OR = 1.73, 95% CI = 1.19 to 2.50, P = 0.004, I² = 0%) and on-demand use of PDE5-Is (OR = 3.32, 95% CI = 2.15 to 5.12, P < 0.00001, I² = 68%).

(Page 13, line 208-211)

In the subgroup analysis, the odds ratio for the incidence of TEAEs for on-demand PDE5-I treatment (OR = 3.44, 95% CI = 1.88 to 6.30, P < 0.00001, I² = 92%) was higher than that for daily PDE5-I treatment (OR = 1.71, 95% CI = 1.17 to 2.49, P = 0.005, I² = 30%).

(Page 13, line 214-217)

The subgroup analysis revealed that the incidence of headache was significantly higher for on-demand PDE5-I treatment (OR = 4.33, 95% CI = 3.09 to 6.08, P < 0.00001, I² = 0%) than for daily PDE5-I treatment (OR = 1.69, 95% CI = 0.98 to 2.91, P = 0.06, I² = 0%).