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ORIGINAL ARTICLE

Prostate Cancer

The therapeutic effect of pelvic floor muscle exercise on urinary incontinence after radical prostatectomy: a meta-analysis

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Pelvic floor muscle exercise (PFME) is the most common conservative management for urinary incontinence (UI) after radical prostatectomy (RP). However, whether the PFME guided by a therapist (G-PFME) can contribute to the recovery of urinary continence for patients after RP is still controversial. We performed this meta-analysis to investigate the effectiveness of G-PFME on UI after RP and to explore whether the additional preoperative G-PFME is superior to postoperative G-PFME alone. Literature search was conducted on Cochrane Library, Embase, Web of Science, and PubMed, to obtain all relevant randomized controlled trials published before March 1, 2018. Outcome data were pooled and analyzed with Review Manager 5.3 to compare the continence rates of G-PFME with control and to compare additional preoperative G-PFME with postoperative G-PFME. Twenty-two articles with 2647 patients were included. The continence rates of G-PFME were all superior to control at different follow-up time points, with the odds ratio (OR) (95% confidence interval [CI]) of 2.79 (1.53–5.07), 2.80 (1.87–4.19), 2.93 (1.19–7.22), 4.11 (2.24–7.55), and 2.41 (1.33–4.36) at 1 month, 3 months, 4 months, 6 months, and 12 months after surgery, respectively. However, there was no difference between additional preoperative G-PFME and postoperative G-PFME, with the OR (95% CI) of 1.70 (0.56–5.11) and 1.35 (0.41–4.40) at 1 month and 3 months after RP, respectively. G-PFME could improve the recovery of urinary continence at both early and long-term stages. Starting the PFME preoperatively might not produce extra benefits for patients at early stage, compared with postoperative PFME.

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Keywords: continence rate; pelvic floor muscle exercise; radical prostatectomy; urinary incontinence

INTRODUCTION

Prostate cancer is a common male cancer and a major cause of cancer-related death in men. It is estimated that nearly one-sixth of men will suffer from prostate cancer over a lifetime.[1] Radical prostatectomy (RP) is the most common therapy for prostate cancer.[2] However, RP may cause some bothersome complications, including the urinary incontinence (UI). The rates of UI after RP differed among various studies, and UI has been reported to happen in more than 80% patients 1 month after RP and 30% patients a year after RP.[3,4] UI after RP immensely affects patients' quality of life and leads to enormous economic burden for patients' families. UI after RP results mainly from urethral sphincter deficiency or detrusor overactivity.[5]

Various therapeutic methods could be used to treat UI, including behavioral treatment, pharmacotherapy, and surgical therapy.[6] Pelvic floor muscle exercise (PFME) is the most common conservative management for UI, which can improve the strength and endurance of striated muscles of the pelvic floor by repeated contractions, partially compensating the urethral sphincter insufficiency.[7] PFME is thought to be an economical and safe therapy for patients.[8] In order to correctly isolate and contract the pelvic floor muscles, patients usually need the guidance of a professional therapist. Moreover, with the guidance and encouragement of a therapist, patients can persist in the exercises for longer time to yield better results.[9] A systematic review indicated that the compliance and adherence of patients were crucial for the efficacy of PFME. Thereby, an effective PFME should be under the guidance and supervision of a professional therapist.[10] It was reported that postoperative PFME guided by a therapist (G-PFME) could hasten the recovery of urinary continence after RP.[11–13] However, several studies showed no beneficial effects of G-PFME, compared with only verbally instructed PFME (V-PFME) or no PFME.[14–16] Whether G-PFME can contribute to the recovery of urinary continence for patients after RP is still controversial at present.

On the other hand, some investigators advocate starting the PFME preoperatively to help patients regain urinary continence. Although numerous studies showed positive results, others indicated that the additional preoperative PFME had limited benefits for patients after RP.[17–19]

We thereby performed this meta-analysis to investigate the effectiveness of G-PFME on UI after RP, and to explore whether the additional preoperative G-PFME is superior to postoperative G-PFME.

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MATERIALS AND METHODS

Literature search

This meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and was registered at International Prospective Register of Systematic Reviews (registration number: CRD42018092219) (**Supplementary Table 1**).

A comprehensive literature search was conducted on Cochrane Library, Embase, Web of Science, and PubMed, to obtain all relevant English articles published before March 1, 2018. The search strategy was: (urinary incontinence) AND (radical prostatectomy) AND (pelvic floor) AND (randomiz*). Cited references of retrieved articles were also screened to gain extra publications. Studies from different databases were reviewed to exclude duplications. Two authors (MLYW and QX) participated in the literature searching process independently to avoid missing useful publications.

Inclusion criteria

Articles meeting the following criteria were included: (1) studies were randomized controlled trials (RCTs); (2) patients were diagnosed with prostate cancer and received RP; (3) the treatment group performed G-PFME while the control group received V-PFME or no PFME, or the treatment group began G-PFME preoperatively while the control group only performed postoperative G-PFME; (4) outcome was the number or percentage of patients regaining urinary continence. Studies with insufficient data were excluded.

Data extraction

The outcome data and primary characteristics of qualified studies were extracted, including the first author, year of publication, sample size, PFME regimens in both treatment group and control group, and follow-up time. The follow-up time was described as months after surgery. If there was more than one treatment group in a study, the patients' number in the control group was divided equally according to the number of treatment groups.[20] To ensure the accuracy and completeness, all data were extracted by two authors (CSW and QX) independently and any discrepancy between the two authors was resolved by discussion.

Quality evaluation

Quality of included studies was evaluated by the Cochrane Collaboration's tool for assessing risk of bias. The tool consists of seven parts: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each part can be graded as low risk of bias, unclear risk of bias, and high risk of bias (**Supplementary Figure 1**).

Statistical analyses

Outcome data were pooled and analyzed with the Review Manager (RevMan) Version 5.3 (The Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, Denmark). As dichotomous data, the outcomes were presented as odds ratio (OR) with 95% confidence interval (CI) at different follow-up time points. Heterogeneity among studies was evaluated by the I^2 test, with $I^2 > 50\%$ considered to be of significant heterogeneity. In case of significant heterogeneity, random effects model was selected to analyze the outcome data and sensitivity analysis was performed to detect the source of heterogeneity, otherwise the fixed effects model was used. Intergroup difference was considered to be statistically significant when $P < 0.05$.

Based on the data we obtained from the qualified studies, we first compared the continence rates of G-PFME with V-PFME or no PFME at different follow-up time points. We defined both the V-PFME and no PFME as control in our study. Then, we compared additional preoperative G-PFME with postoperative G-PFME.

RESULTS

Eligible studies

Initially, 336 publications were searched from databases and other resources (**Figure 1**). After screening, 22 RCTs with 2647 patients were included in our study.[11–19,21–33] All articles measured and compared the continence rates of patients in different groups, with the follow-up time ranging from 1 month to 1 year (**Table 1**). The definitions of continence were different among studies, with ten studies defining continence based on the number of pads used daily, eight based on the 24-h pad test, two based on bladder diary, and two based on the International Consultation on Incontinence Questionnaire on Urinary Incontinence (ICIQ-UI). Fifteen trials tested the effectiveness of postoperative G-PFME that started after catheter removal. The other seven trials investigated preoperative G-PFME beginning about 4 weeks before surgery and continuing after catheter removal, in which two trials compared preoperative G-PFME with postoperative G-PFME. The treatment regimen in different studies included G-PFME, G-PFME with biofeedback, and G-PFME combined with electrical stimulation. The control groups received no PFME or just V-PFME.

Quality of included studies

Altogether, most studies were of moderate-to-high quality according to the Cochrane Collaboration's tool for assessing risk of bias (**Figure 2**). Fourteen studies performed the randomization with computer-generated random numbers, while the others did not explain the randomization methods. Moreover, nearly half of these studies concealed the allocation strategies. The treatment regimens in treatment group and control group were distinct; therefore, both the intervenors and patients were not blinded. However, the outcome assessors were blinded to the grouping and treatment in some trials. All studies conducted the follow-up investigations systematically and carefully and explained the reasons for dropout. No selective report existed in these trials. In addition, 12 studies calculated the sample size to increase the power of test.

Effectiveness of PFME on UI after RP

G-PFME could improve the recovery of urinary continence at both early (**Figure 3**) and long-term (**Figure 4**) stages. The follow-up time points were different among studies. We pooled and analyzed the

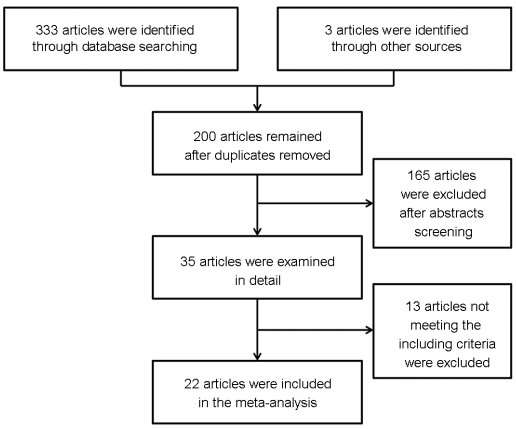

Figure 1: Flow diagram of trial selection process.

Table 1: Characteristics of included studies

Study	*Year*	*Sample size (n)*	*Definition of continence*	*Treatment regimen*	*Control*	*Follow-up time after surgery (month)*
Ahmed *et al.*[21]	2012	80	Pad free	Postoperative G-PFME with ES Postoperative G-PFME with ES and BF	Postoperative V-PFME	3, 6
Aydın Sayılan and Özbaş[17]	2018	60	Pad free	Preoperative G-PFME	No PFME	1, 3, 6
Bales *et al.*[18]	2000	100	Use of ≤1 pad	Preoperative G-PFME with BF	Preoperative V-PFME	1, 2, 3, 4, 6
Burgio *et al.*[22]	2006	102	Based on bladder diary	Preoperative G-PFME with BF	No PFME	3, 6
Centemero *et al.*[19]	2010	118	Based on bladder diary	Preoperative G-PFME	Postoperative G-PFME	1, 3
Dubbelman *et al.*[14]	2010	66	<4 g on 24-h pad test	Postoperative G-PFME	Postoperative V-PFME	1, 2, 3, 6
Dijkstra-Eshuis *et al.*[23]	2015	103	0 g on 24-h pad test	Preoperative G-PFME with BF	Postoperative V-PFME	12
Filocamo *et al.*[13]	2005	300	Use of ≤1 pad	Postoperative G-PFME	No PFME	1, 3, 6, 12
Franke *et al.*[15]	2000	23	Pad free	Postoperative G-PFME with BF	No PFME	3, 6
Geraerts *et al.*[24]	2013	170	0 g on 24-h pad test	Preoperative G-PFME with BF	Postoperative G-PFME with BF	1, 3, 6, 12
Glazener *et al.*[16]	2011	391	Based on questionnaire	Postoperative G-PFME	No PFME	3, 6, 9, 12
Van Kampen *et al.*[25]	2000	98	≤2 g on 24-h pad test	Postoperative G-PFME with BF	No PFME	1–12
Manassero *et al.*[12]	2007	94	≤2 g on 24-h pad test	Postoperative G-PFME	No PFME	1, 3, 6, 12
Marchiori *et al.*[26]	2010	332	Pad free	Postoperative G-PFME with ES and BF	Postoperative V-PFME	3, 6, 12
Mariotti *et al.*[27]	2009	60	≤2 g on 24-h pad test	Postoperative G-PFME with ES and BF	Postoperative V-PFME	1–6
Moore *et al.*[28]	2008	205	≤8 g on 24-h pad test	Postoperative G-PFME with BF	Postoperative V-PFME	2, 3, 4, 7, 12
Overgård *et al.*[29]	2008	80	Pad free	Postoperative G-PFME	Postoperative V-PFME	3, 6, 12
Parekh *et al.*[30]	2003	38	Use of ≤1 pad	Preoperative G-PFME with BF	No PFME	3, 4, 5, 7, 12
Pedriali *et al.*[31]	2016	85	Pad free	Postoperative G-PFME postoperative G-PFME with ES	No PFME	4
Ribeiro *et al.*[32]	2010	54	Use of ≤1 pad	Postoperative G-PFME with BF	Postoperative V-PFME	1, 3, 6, 12
Tienforti *et al.*[11]	2012	32	Based on questionnaire	Postoperative G-PFME with BF	Postoperative V-PFME	1, 3, 6
Yamanishi *et al.*[33]	2010	56	≤8 g on 24-h pad test	Postoperative G-PFME with ES	Postoperative V-PFME	1, 3, 6, 12

PFME: pelvic floor muscle exercise; G-PFME: pelvic floor muscle exercise guided by a therapist; ES: electrical stimulation; BF: biofeedback; V-PFME: verbally instructed pelvic floor muscle exercise

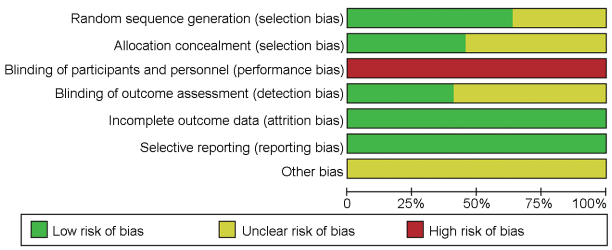

Figure 2: Risk of bias of included studies.

outcome data at 5 frequently used time points: 1 month, 3 months, 4 months, 6 months, and 12 months after surgery, separately. Ten articles measured the continence rate at the first month after surgery, showing that the OR between G-PFME group and control group was 2.79 (95% CI: 1.53–5.07, $P = 0.0008$). At 3 months, 4 months, and 6 months after the surgery, the ORs were 2.80 (95% CI: 1.87–4.19; $P < 0.0001$), 2.93 (95% CI: 1.19–7.22; $P = 0.02$), and 4.11 (95% CI: 2.24–7.55; $P < 0.0001$), respectively. After 1 year, the continence rate was still remarkably higher in G-PFME group, compared with control group, with the OR as 2.41 (95% CI: 1.33–4.36; $P = 0.004$).

We next explored whether additional preoperative G-PFME was better than postoperative G-PFME. Although there were seven articles investigating additional preoperative G-PFME, most of them compared preoperative G-PFME with postoperative V-PFME or no PFME. Only two studies set postoperative G-PFME as control group. We pooled data from these two articles and found that there was no apparent difference between additional preoperative G-PFME and postoperative G-PFME, with the OR as 1.70 (95% CI: 0.56–5.11; $P = 0.35$) and 1.35 (95% CI: 0.41–4.40; $P = 0.62$) at 1 month and 3 months after RP, respectively (**Figure 5**). However, this result was not so convincing due to the limited number of studies.

DISCUSSION

Our meta-analysis showed that G-PFME could hasten the recovery of urinary continence for patients after RP at both early and long-term stages. This suggested that G-PFME was an effective treatment strategy for UI and should be recommended to patients. A further analysis showed that, compared with postoperative G-PFME, starting the G-PFME before surgery did not bring remarkable extra benefits for patients. Whether patients should begin G-PFME preoperatively needs further research.

The mechanism of how PFME rescues UI is that repeated voluntary contraction of the pelvic floor muscles can enhance their strength and endurance. Several striated muscles can influence the urethral pressure, including the striated urethral rhabdosphincter, the bulbocavernosus, and the levator ani muscle.[34] Some verbal or written instructions were used to train patients to perform PFME, such as "elevate the penis," "tighten the anus," and "stop the uroflow."[35] These different verbal instructions lead to the contraction of different pelvic floor muscles.[36] Because of the complexity of the anatomy of pelvic floor muscles, it is difficult for patients to judge which muscle is contracted and whether the contraction is correct. Moreover, avoiding the contraction of abdominal muscles during PFME is also a challenge for patients. Thereby, an effective PFME need the guidance of a professional therapist who can teach patients perform correct exercises with digital anal palpation or biofeedback devices. Transabdominal real-time ultrasound imaging could also be used to visualize the structures of pelvic floor and help patients isolate muscle activation. No matter which

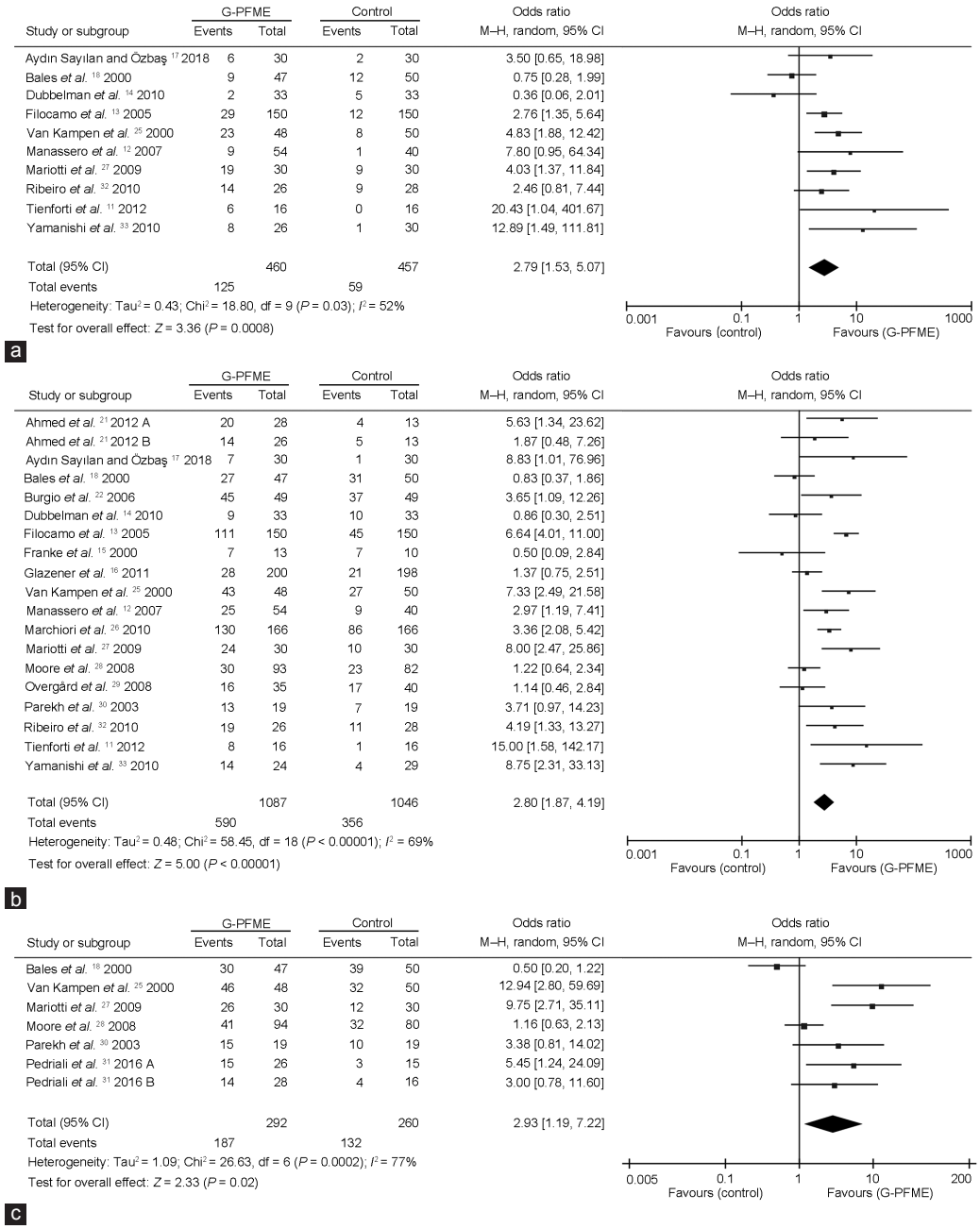

Figure 3: Forest plot comparing G-PFME with control at 1 month, 3 months, and 4 months after surgery. (**a**) Forest plot comparing G-PFME with control at 1 month after surgery. (**b**) Forest plot comparing G-PFME with control at 3 months after surgery. (**c**) Forest plot comparing G-PFME with control at 6 months after surgery. A or B: if a study has two treatment groups, then one treatment group is named as A and the other treatment group is named as B. G-PFME: pelvic floor muscle exercise guided by a therapist; CI: confidence interval; df: degrees of freedom; M–H: Mantel–Haenszel.

guidance method was used, the purpose of G-PFME was to achieve correct and effective muscle contraction. Moreover, the guidance and supervision of a therapist can help patients to keep on performing the exercise. On the contrary, the PFME with only verbal/written instructions was thought to be useless and was treated as control group in most studies.

Before conducting PFME, a therapist should explain the anatomy and function of pelvic floor muscles to patients. Then patients are trained to contract the pelvic floor muscles correctly. After that, patients are requested to conduct the PFME daily at different positions, including supine position, sitting, standing, and squatting. Patients are also encouraged to practice PFME before activities which may induce leakage of urine, such as coughing, sneezing and lifting heavy things. In addition, patients need to pay a return visit to the therapist at regular intervals to adjust exercise methods.

PFME could decrease the incontinent episodes in older women and men with stress and urge incontinence.[37] Some studies also showed that PFME were effective for UI after RP.[32,33] Thereby, PFME was usually recommended for treating UI after RP. However, its effectiveness is still controversial at present. Glazener *et al*.[16] reported that the UI rate was not apparently different between the intervention group receiving a four-session G-PFME and control group with standard care. Their

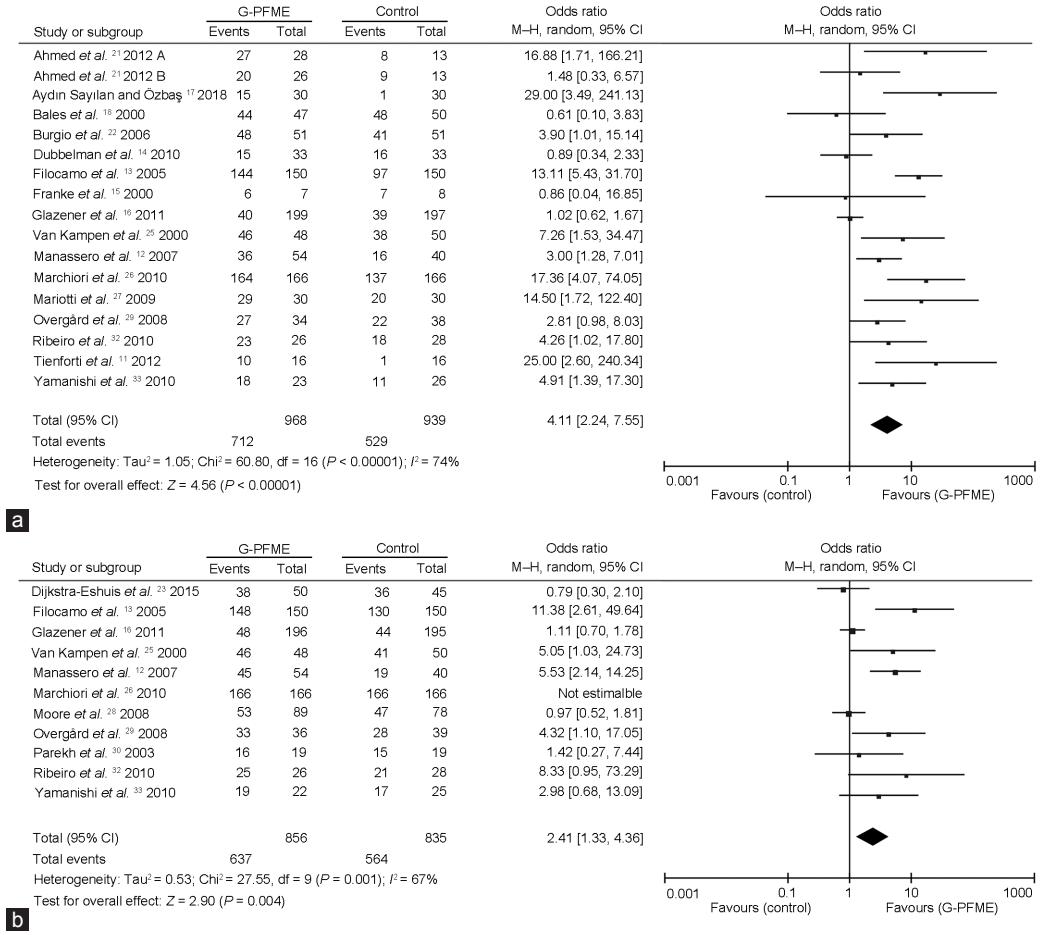

Figure 4: Forest plot comparing G-PFME with control at 6 months and 12 months after surgery. (**a**) Forest plot comparing G-PFME with control at 6 months after surgery. (**b**) Forest plot comparing G-PFME with control at 12 months after surgery. A or B: if a study has two treatment groups, then one treatment group is named as A and the other treatment group is named as B. G-PFME: pelvic floor muscle exercise guided by a therapist; CI: confidence interval; df: degrees of freedom; M–H: Mantel–Haenszel.

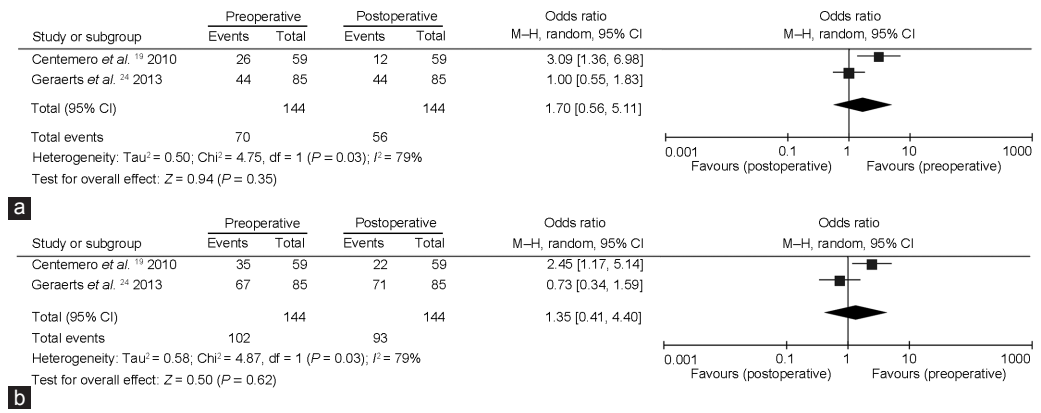

Figure 5: Forest plot comparing preoperative G-PFME with postoperative G-PFME at 1 month and 3 months after surgery. (**a**) Forest plot comparing preoperative G-PFME with postoperative G-PFME at 1 month after surgery. (**b**) Forest plot comparing preoperative G-PFME with postoperative G-PFME at 3 months after surgery. G-PFME: pelvic floor muscle exercise guided by a therapist; CI: confidence interval; df: degrees of freedom; M–H: Mantel–Haenszel.

explanation was that the information about PFME was widely available and patients in the control group might also have conducted the PFME by themselves. Similarly, a study by Dubbelman *et al.*[14] showed that G-PFME had no beneficial effect on the regain of continence. The authors attributed the negative results to insufficient sample size. Bales *et al.*[18] thought that a more frequent and intensive PFME program would produce a better outcome. Our meta-analysis collected all the available RCTs in regard to PFME and UI after RP up to date, in order to obtain more compelling evidence. Our result verified that G-PFME was an effective and lasting strategy for UI after RP, because the continence rate was higher in G-PFME group than that in control group at 1 month, 3 months, 4 months, 6 months, and 12 months after surgery.

To improve the efficacy of PFME, some researchers attempted to train patients to conduct PFME preoperatively. Burgio *et al*.[22] pointed out that initiating PFME preoperatively could make patients more prepared for the exercise. Besides, patients could learn how to contract the pelvic floor muscles with full sensation and without pain if they started the PFME preoperatively. Their study indicated that preoperative PFME could hasten the regain of continence and reduce the severity of UI. Chang and colleagues[3] conducted a meta-analysis to evaluate the effect of additional preoperative PFME on postprostatectomy UI, demonstrating that preoperative PFME improved the early but not long-term continence rates. Since both preoperative PFME and postoperative PFME were reported to be beneficial in some studies, which one should be chosen for patients? Centemero *et al*.[19] reported that preoperative PFME could improve early recovery of continence compared with postoperative PFME. On the contrary, a study by Geraerts *et al*.[24] indicated that starting PFME before surgery did not produce better results than starting PFME after catheter removal. Therefore, we performed the meta-analysis to resolve this disagreement. After pooling data from two studies, we found that additional preoperative PFME did not hasten the recovery of continence at 1 month and 3 months after RP, compared with postoperative PFME. However, this finding should be interpreted cautiously due to the limited number of studies. Furthermore, as the preoperative PFME in these two studies began 3 or 4 weeks before the surgery, it was not clear whether starting the PFME more early would produce better results. Further investigations were essential to resolve this issue.

Our meta-analysis included enough studies and most studies had low risk of bias. Nevertheless, the study is limited by the heterogeneity of included studies, which was caused by multiple factors. First of all, the type of treatment regimens varied among studies, including the way to guide PFME (palpation, biofeedback devices, or ultrasound), the frequency of PFME, and the length of PFME. In addition, the definition of continence differed between trials, such as pad free, no leakage based on bladder diary, and no more than 4 g urine on 24-h pad test. These differences were inevitable as there is no standard treatment regimen and precise definition of continence at present. Sensitivity analysis was conducted by removing the included studies one by one to detect the source of heterogeneity. However, no study was found to be responsible for the heterogeneity. Thereby, we could only perform our meta-analysis with the random effect model to reduce the influence of heterogeneity.

CONCLUSIONS

This meta-analysis demonstrates that G-PFME could hasten the recovery of UI after RP at both early and long-term stages. We thereby recommend G-PFME to patients after RP to regain continence early. Starting the PFME 1 month before the surgery might have no extra benefits compared with postoperative PFME. However, this result requires further investigations.

AUTHOR CONTRIBUTIONS

MLYW and QX searched and selected studies. CSW and QX extracted and analyzed the data. MLYW and TYZ drafted the manuscript. MLYW, CHP, and TYZ revised the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

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Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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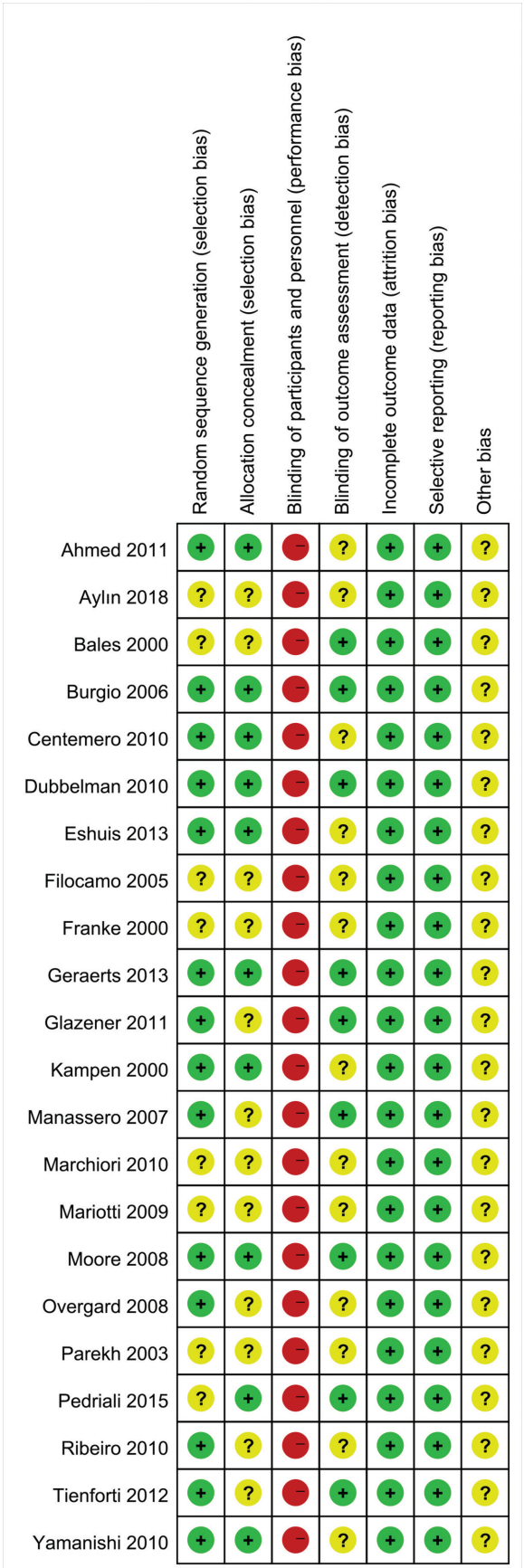

Supplementary Figure 1: Risk of bias summary.

Supplementary Table 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist

Section/topic	*#*	*Checklist item*	*Reported on page #*
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	1
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	1
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	1
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale	2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means)	2
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis	2
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies)	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	NA
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations	2,3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12)	2,3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot	2-5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	2-5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15)	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16])	NA
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers)	3-6
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias)	6
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	6
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review	6