·临床研究·

他达拉非5 mg治疗前列腺增生继发下尿路症状的荟萃分析

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【摘 要】 目的 评价他达拉非(tadalafil)5 mg治疗前列腺增生继发下尿路症状(BPH/LUTS)的疗效及安全性。**方法** 计算机及手工检索相关的随机对照研究(RCTs)。计算机检索时间限定为数据库建立至2018年10月,数据库包括万方数据库、中国期刊全文数据库(CNKI)、中国科技期刊数据库(VIP)、中国生物医学文献数据库(CBM),EMBASE、PubMed、Cochrane Library、Clinicaltrials.gov。对符合纳入标准的研究进行质量评估,提取数据并使用RevMan 5.3软件进行荟萃分析。**结果** 本次分析纳入9个RCTs,共计3501例患者,其中他达拉非5 mg组1758例,安慰剂对照组1743例。与安慰剂组相比,他达拉非5 mg组可降低国际前列腺症状评分(IPSS)[*MD*=-1.79,95%*CI*(-2.19, -1.39)],改善生活质量(IPSS-Qol)[*MD*=-0.26,95%*CI*(-0.36, -0.16)],但对最大尿流率(Qmax)没有明显改善[*MD*=0.15, 95%*CI*(-0.35, 0.64), *P*=0.55]。与安慰剂组相比,他达拉非5 mg组不会明显增加因不良事件而退出的患者比例[*RR*=1.54,95%*CI*(0.96, 2.49),*P*=0.08,I^2=0%]。**结论** 他达拉非5 mg治疗前列腺增生可改善患者的下尿路症状,并具有良好的耐受性。

【关键词】 他达拉非;前列腺增生;下尿路症状;荟萃分析

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A meta-analysis of tadalafil 5 mg for treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia

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【Abstract】 Objective To evaluate the efficacy and safety of tadalafil 5 mg in the treatment of lower urinary tract symptoms (LUTS) in men with benign prostatic hyperplasia (BPH). **Methods** Randomized controlled trials (RCTs) were collected *via* computer-based and manual retrieval. The computer retrieval was limited to the time of database establishment until October 2018, and no limit was set for langauge. The databases searched included Wanfang database, China Journal Full-text Database (CNKI), China Science and Technology Periodical Database (VIP), China Biomedical Literature Database (CBM), EMBASE, PubMed, Cochrane. Library, and Clinicaltrials.gov. Quality assessments were performed for studies that met the inclusion criteria, data were extracted, and a meta-analysis was performed using RevMan 5.3. **Results** Included for analysis were 9 RCTs with a total of 3501 patients, 1758 being treated with the tadalafil 5 mg and 1743 with placebo. Compared with placebo, tadalafil 5 mg reduced the International Prostate Symptom Score (IPSS) [*MD*=-1.79, 95%*CI* (-2.19, -1.39)], improved quality of life (IPSS-Qol) [*MD*=-0.26, 95%*CI* (-0.36, -0.16)], but did not lead to significant improvement in maximum urinary flow rate (Qmax) [*MD*=0.15, 95%*CI* (-0.35, 0.64), *P*=0.55]. The proportion of patients who withdrew due to adverse events was not significantly increased in the tadalafil 5 mg group [*RR*=1.54, 95%*CI* (0.96, 2.49), *P*=0.08, I^2=0%]. **Conclusion** Tadalafil 5 mg can improve the LUTS in the patients with BPH and is well tolerated.

【Key words】 tadalafil; benign prostatic hyperplasia; lower urinary tract symptoms; meta-analysis

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前列腺增生继发下尿路症状(lower urinary tract symptoms suggestive of benign prostatic hyperplasia, LUTS/BPH)作为一种排尿障碍性疾病,呈现出明显的年龄相关性。有研究表明,组织学 BPH 的发病率在 60 岁时为 50%,80 岁时高达 83%[1],而 50%的组织学诊断 BPH 患者伴有下尿路症状[2]。在不同种族背景下 LUTS 和阳痿(erectile dysfunction, ED)有着高度的相关性[3-8],并且 LUTS 的严重程度与 ED 发生频率呈正比[7,9,10],影响患者的身体活动、性关系、社会生活和未来健康[11,12]。α 受体阻滞剂(α-blockers, αBs)联合使用 5α 还原酶抑制剂(5α-reductase inhibitors, 5αRIs),可获得改善 LUTS 的满意效果[13]。但使用 αBs 以及 5αRIs 可能引起性功能障碍的副作用,且其不会改善与 LUTS 相关的性功能障碍,甚至会使症状加重[14]。

5 型磷酸二酯酶抑制剂(phosphodiesterase type 5 inhibitors, PDE5-Is)通过抑制 5 型磷酸二酯酶(phosphodiesterase type 5, PDE5)介导的环鸟苷酸(cyclic guanosine monophosphate, cGMP)分解而放大一氧化氮/环鸟苷酸(NO/cGMP)通路的功能,引起平滑肌松弛。研究发现人类膀胱逼尿肌、前列腺、尿道壁均表达有 PDE5[15-17],并对平滑肌的收缩、血管内皮功能、盆腔血流灌注起调节作用[18-23]。PDE5-Is 治疗 BPH/LUTS 的可能机制包括:增加下尿路(lower urinary tract, LUT)局部的氧合功能,调节其血流灌注;松弛膀胱颈及前列腺的平滑肌;调控 LUT 基质成分的增殖和分化;减弱膀胱传入神经活动;控制 LUTS 相关的炎症[24]。已有学者在临床中应用 PDE5-Is 治疗下尿路症状并观察到了国际前列腺症状评分(International Prostate Symptom Score, IPSS)的改善[25-27],此外在一项西地那非和阿呋唑嗪联合应用治疗下尿路症状的研究中,观察到了相较于传统联合用药更高的 IPSS 改善[28],更加支持了 PDE5-Is 可能是治疗 BPH/LUTS 的潜在药物。

他达拉非是环磷酸鸟苷(cGMP)特异性磷酸二酯酶 5(PDE5)的选择性、可逆抑制剂。本次研究的主要目的是通过循证医学的原理和方法,应用荟萃分析评价他达拉非 5 mg 治疗 BPH/LUTS 的有效性和安全性,为临床治疗 BPH/LUTS 决策制定提供一定的参考。

1 资料与方法

1.1 研究资料

纳入标准:(1)随机安慰剂平行对照研究;(2)患者为年龄>40 岁、确诊为 LUTS/BPH、伴或不伴有 ED 的男性(将患者年龄限定为>40 岁,是因为 LUTS/BPH 多发于中老年男性,而在青年男性中发病率较低[29]);(3)干预措施为单药应用他达拉非 5 mg 治疗 BPH/LUTS;应至少包含 IPSS 以及因不良事件退出研究患者人数的相关结局。排除标准:(1)非中英文的研究;(2)无法获取分析所需要信息的研究;(3)相同原始研究的事后分析,析因分析以及重复发表的研究。

1.2 方法

1.2.1 检索策略 计算机检索万方数据库、中国期刊全文数据库(CNKI)、中国科技期刊数据库(VIP)、中国生物医学文献数据库(CBM), EMBASE、PubMed、Cochrane Library、Clinicaltrials. gov,检索时间设定为数据库建立至 2018 年 10 月。中文检索词包括“他达拉非”,“前列腺增生”,“下尿路症状”,“随机”,“双盲试验”等;英文检索词包括“tadalafil”,“LUTS”,“BPH”,“randomized controlled trial”等。同时手工翻阅文献资料,寻找相关研究。

1.2.2 研究的质量评估 对纳入研究可能存在的偏倚风险进行以下 6 个条目的评估:选择性偏倚、实施偏倚、测量偏倚、随访偏倚、不完整数据、报告偏倚、其他偏倚。评估结果汇总于偏倚风险评估表和偏倚风险总结表。

1.2.3 数据提取 提取研究基本信息:研究文献 ID(第一作者加时间)或试验注册号、研究年限、研究地点、样本量、实验组及对照组细节、研究持续时间以及纳入对象的情况(年龄、IPSS、入选条件等)。结局指标包括:IPSS、前列腺症状相关生活质量评分(IPSS quality of life, IPSS-Qol)、最大尿流率(maximal urinary flow, Qmax)、因不良事件退出研究的患者例数和研究期间出现的不良事件(treatment-emergent adverse events, TEAES)。

1.2.4 证据质量评价 采用 GRADEpro 证据分级评价系统对荟萃分析结果进行质量评价,评价内容包括:(1)研究自身是否存在局限性;(2)研究结局是否一致,是否存在无法解释的异质性;(3)证据是否间接获得;(4)结果是否精确;(5)是否存在发表偏倚的高度可能性。根据如上问题的相应回答将质量评价结果分为高、中、低、极低 4 个等级,并通过质量评估表呈现。

1.3 统计学处理

本次分析依据 Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0[30] 提供的方法,使用 ReVman 5.3 软件进行数据分析。选择随机效应模型对所收集的结局统计量进行分析,应用

倒方差模型处理连续性变量,Mantel-Haenszel 模型处理二分类变量,并提供结果的95%置信区间。异质性大小根据森林图各置信区间重叠情况和统计量 I^2 加以量化,0%<I^2<40%时,认为各研究间异质性较低[31]。若研究间异质性较高,我们将进行敏感性分析,寻找异质性来源并加以解决。由于本次分析纳入研究数量<10,我们未采用漏斗图分析可能存在的发表偏倚。

2 结 果

2.1 文献检索结果

本次分析检索文献 318 篇,其中计算机检索318 篇,手工检索 0 篇。使用 EndnoteX7 软件筛除重复文献 137 篇,2 名研究员分别独立浏览文献标题和摘要内容,筛除不相关研究 148 篇。随后对剩余文献进行全文浏览,排除正在进行的研究 1 篇,重复数据的二次分析 21 篇,最后将 9 个随机对照试验(randomized controlled trials, RCTs)[32-41]纳入本次荟萃分析,研究的筛选流程详见图 1。

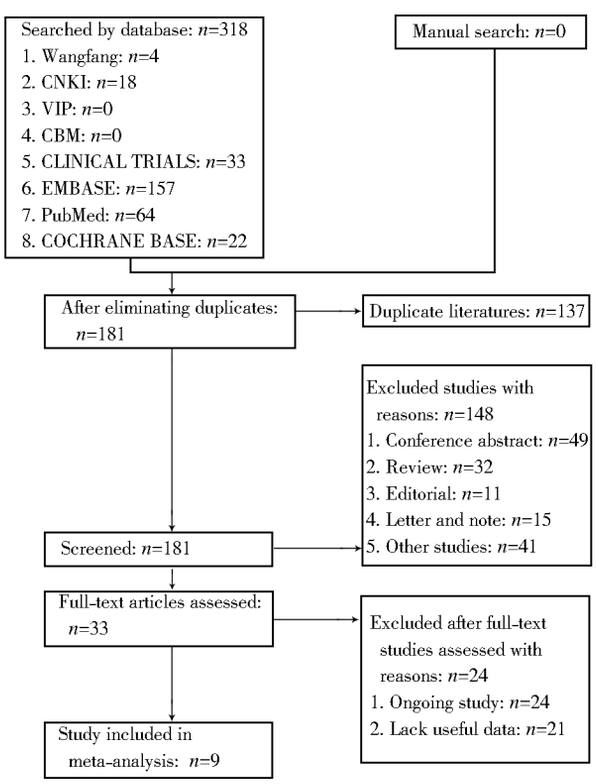


图 1 文献筛选流程图

Figure 1 Flow diagram of studies selection process

2.2 纳入研究的偏倚风险评估

本次纳入的 9 个 RCTs 中,仅能获取少量关于患者随机分组和分配隐藏的确切信息。大部分研究提及了整个研究过程使用双盲的方法,但未给出更多相关细节。尽管从全部研究获取了本次分析所需要的结局信息,然而通过比对研究注册号和公开的计划书,我们发现大多数研究存在选择性报告。对以上结果进行综合评估后,将本次纳入研究的整体偏倚风险确定为偏倚风险不清楚。结果详见偏倚风险评估表(图 2)和偏倚风险总结表(图 3)。

2.3 纳入研究的基线信息

所有研究入组患者年龄≥45 岁,均有中等严重程度的下尿路症状,既往史无明显差异,双盲研究周期 12 周,IPSS≥13,均口服给药,1 次/d。2 个研究[32,40]限定入组患者必须有性活动或性愿望,4 个研究[37-40]将人群限定为亚洲。更多研究细节详见表 1。

2.4 荟萃分析结果

2.4.1 主要结局指标荟萃分析 与安慰剂组相比,他达拉非 5 mg 组可改善 IPSS[MD=-1.79, 95%CI(-2.19, -1.39), I^2=0%]和 IPSS-Qol[MD=-0.26, 95%CI(-0.36, -0.16), I^2=0%],但最大尿流率(Qmax)[MD=0.15, 95%CI(-0.35, 0.64), P=0.55, I^2=43%]2 组无统计学差异。详见图 4。各指标的证据等级评定见表 2。

由于 Qmax 指标 I^2>40%,故对 Qmax 的结果行敏感性分析。去除两个效应方向明显相反的研究(Takeda2012、Yokoyama2012)后,分析结果为[MD=0.52, 95% CI(0.08, 0.97), P=0.02, I^2=0%]。敏感性分析结果和原分析结果差异大,无法确定这种差异来自真正的效应差异或是偏倚混杂。我们将该证据等级评定为极低,降级原因为:研究自身限制,研究间存在异质性(I^2=43%)和结果不精确(置信区间过宽)。

2.4.2 试验中因不良事件退出的患者比例 他达拉非 5 mg 组和安慰剂组相比,不会明显增加因不良事件而退出的患者比例[RR=1.54, 95%CI(0.96, 2.49), P=0.08, I^2=0%](图 5)。每 1 000 例使用他达拉非 5 mg 治疗的患者将增加 9 例因不良事件而退出治疗的患者数[95%CI(-1, 24)]。

2.4.3 不良事件 9 个 RCTs 均详细描述了试验中出现的不良事件,其中头痛、消化不良、背痛、肌痛及鼻咽炎是报告最多的不良事件(表 3)。所有研究均未报告实验室检查及生命体征出现明显变化。所有研究均未报告与心脑血管或性功能异常相关的不良事件。1 个研究报告了 1 例患者出现了急性尿潴留并实施了留置导尿。

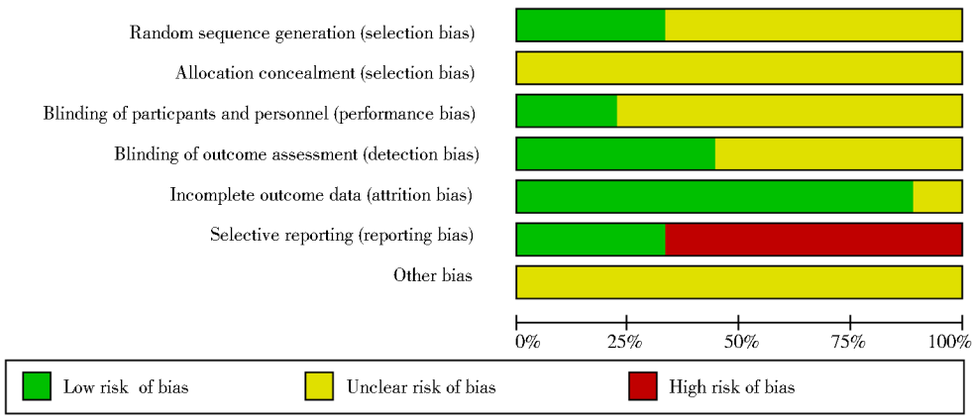


图 2 偏倚风险评估表

Figure 2 Graph of risk of bias

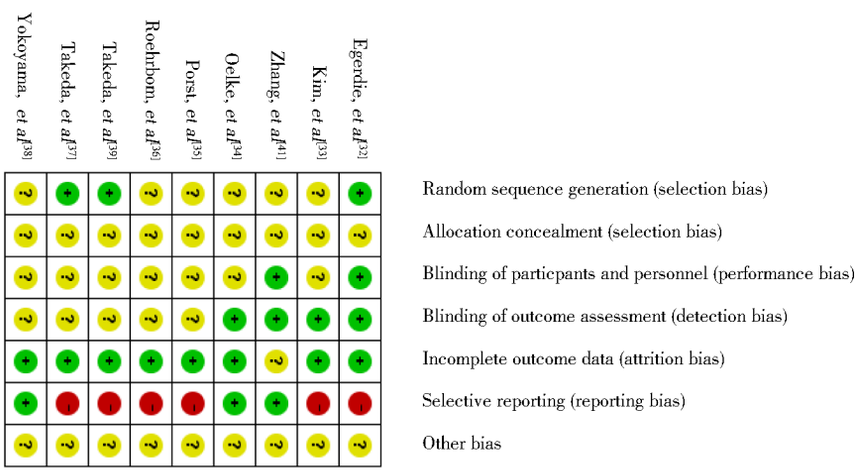


图 3 偏倚风险总结表

Figure 3 Summary of risk of bias

3 讨 论

虽然在临床应用 αBs 和 5αRIs 治疗 BPH/LUTS 取得了不错的治疗效果，并且在联合两者使用时可获得更好的症状改善，但是联合治疗也与较高的不良事件发生率相关[42]。应用药物治疗 BPH/LUTS 时，患者的依从性在诊疗过程中扮演了十分重要的角色。患者对 αBs 和 5αRIs 主导的治疗策略表现出较差的依从性，联合应用 αBs 和 5αRIs 治疗的 BPH/LUTS 患者，随访 12 个月后仅有 9% 的患者继续治疗[43]。高选择性 αBs 减少了血管相关不良反应发生，但与性功能相关的不良反应明显增加[14]，药物的不良反应无疑会降低患者的依从性，直接影响临床结果[43]，因此对于现有药物治疗策略的调整依然十分必要。

本次分析结果显示，使用他达拉非 5 mg 可降低 IPSS 评分并表现出良好的耐受性，且所有入选研究均未出现与性功能障碍相关的不良反应。而一篇专门探讨药物治疗 BPH/LUTS 同男性射精功能障碍关系的荟萃分析显示，无论应用 αBs 或者 5αRIs 均会明显增加患者出现射精异常的风险[14]，对于存在上述性功能障碍的 BPH/LUTS 患者而言，他达拉非 5 mg 会减少患者因不良反应而产生的治疗顾虑。男性 BPH/LUTS 同 ED 存在着高度相关性，这种相关性同 LUTS 的严重程度以及患者年龄成正比[7,9,10]，PDE5-Is 作为一种治疗 ED 的药物，它的效果已经得到临床的肯定，他达拉非相较其同类药物有着更好的 ED 改善效果[44]，而在本次分析纳入的研究中也提示他达拉非 5 mg 在缓解患者 LUTS 的同时也可以改善其 ED 症状[32,35,36,41]。

表1 纳入研究的基线特征

Table 1 Study and patient characteristics

Study	Trial period	Country	Total sample(n)	Description of participants	Sbjects group		
					Intervention	Age(years)	IPSS
Roehrborn, *et al*[36]	2006.08-2008.10	Europe	1058	Qmax 4-15 ml/s,	Tadalafil 2.5 mg	62.0	17.5±5.8
		United States		PVR<300 ml, MVV≥125 ml,	Tadalafil 5 mg	61.9	17.3±6.0
				PSA<10 ng/ml*,	Tadalafil 10 mg	62.2	17.8±5.6
				BPH/LUTS≥6 months,	Tadalafil 20 mg	62.5	17.1±6.5
				with ED or not	Placebo	61.7	17.1±6.4
Egerdie, *et al*[32]	2009.03-2010.10	Europe	606	Qmax 4-15 ml/s, PVR<300 ml,	Tadalafil 2.5 mg	62.5	18.2±5.6
				BPH/LUTS>6 months,	Tadalafil 5 mg	62.2	18.5±5.8
				with ED≥3 months	Placebo	62.9	18.2±5.3
Kim, *et al*[33]	2007.10-2008.06	South Korea	151	Qmax 4-15 ml/s, PVR<300 ml,	Tadalafil 5 mg	61.2	17.1±5.4
				BPH/LUTS>6 months,	Tamsolusin 0.2 mg	61.5	17.7±5.0
				PSA<10 ng/ml, with ED or not	Placebo	62.2	17.3±5.0
Oelke, *et al*[34]	2009.10-2011.01	Australia	511	Qmax 4-15 ml/s, MVV≥125 ml,	Tadalafil 5 mg	63.5	17.2±4.9
		Europe		BPH/LUTS>6 months,	Tamsolusin 0.4 mg	63.5	16.8±5.3
		United States		with ED or not	Placebo	63.7	17.4±6.0
Porst, *et al*[35]	2009.01-2009.11	Australia	325	Qmax 4-15 ml/s, PVR<300 ml,	Tadalafil 5 mg	65.1	17.1±6.1
		Europe		PSA<10 ng/ml, BPH/LUTS>	Placebo	64.6	16.6±6.0
		America		6 months, with ED or not			
Yokoyama, *et al*[38]	2009.03-2010.06	Taiwan	612	Qmax 4-15 ml/s, PVR<300 ml,	Tadalafil 2.5 mg	63.7	16.6±6.5
		South Korea		PSA<10 ng/ml, TPV≥20 ml,	Tadalafil 5 mg	62.3	17.2±6.0
		Japan		BPH/LUTS>6 months,	Tamsolusin 0.2 mg	62.6	16.6±6.4
				with ED or not	Placebo	63.7	16.8±6.1
Takeda, *et al*[37]	2011.09-2012.10	South Korea	610	Qmax 4-15 ml/s,	Tadalafil 5 mg	60.8	18.7±6.0
		Japan		PVR<300 ml, MVV≥125 ml,	Placebo	60.9	18.7±5.2
				PSA<10 ng/ml, TPV≥20 ml			
Takeda, *et al*[39]	2008.09-2010.04	Japan	422	Qmax 4-15 ml/s,	Tadalafil 2.5 mg	67.0	16.3±6.5
				PVR<300 ml, MVV≥125 ml,	Tadalafil 5 mg	67.4	16.4±5.9
				PSA<10 ng/ml, TPV>20 ml	Placebo	67.4	16.5±5.4
Zhang, *et al*[41]	2013.09-2015.12	China	909	Sexually active,	Tadalafil 5 mg	61.8	18.4±6.3
				PSA<10 ng/ml,	Tamsolusin 0.2 mg	61.9	18.4±6.7
				BPH/LUTS with ED	Placebo	61.8	18.4±6.1

BPH: benign prostatic hyperplasia; ED: erectile dysfunction; IPSS: International Prostate Symptom Score; LUTS: lower urinary tract symptoms; MVV: minimum voided volume; PSA: prostate-specific antigen; PVR: postvoid residual volume; Qmax: maximal urinary flow rate; TPV: total prostate volume. *: When the prostate specific antigen is 4-10 ng/ml, it is necessary to continuously observe the prostate biopsy within 12 months.

尽管本次研究采用了敏感性较高的检索策略，但仍有可能由于存在一些灰色文献而遗漏相关研究。由于未采用漏斗图对可能存在的发表偏倚进行评估，无法获知可能存在的发表偏倚对本次分析结果的影响。我们尝试联系研究的相关作者，以获得关于研究的更多信息，但并未得到相关作者回复，这可能成为本次分析偏倚的来源。

在临床实践中药物治疗 BPH/LUTS 是一个长期过程，由于本次荟萃分析的研究均为短期随访（12周），分析结果显示的短期有效性及安全性可能不足以保证长期结果的一致性，同时对不良反应的了解可能存在局限。治疗 BPH/LUTS 应合理平衡治疗收益和副作用，结合当地医疗资源的分配考虑患者的经济状况，充分尊重患者的治疗意愿是十分必要的。对于无法耐受传统治疗药物副反应、而又不具备手术治疗绝对适应证的患者，他达拉非 5 mg 不失为一种选择。

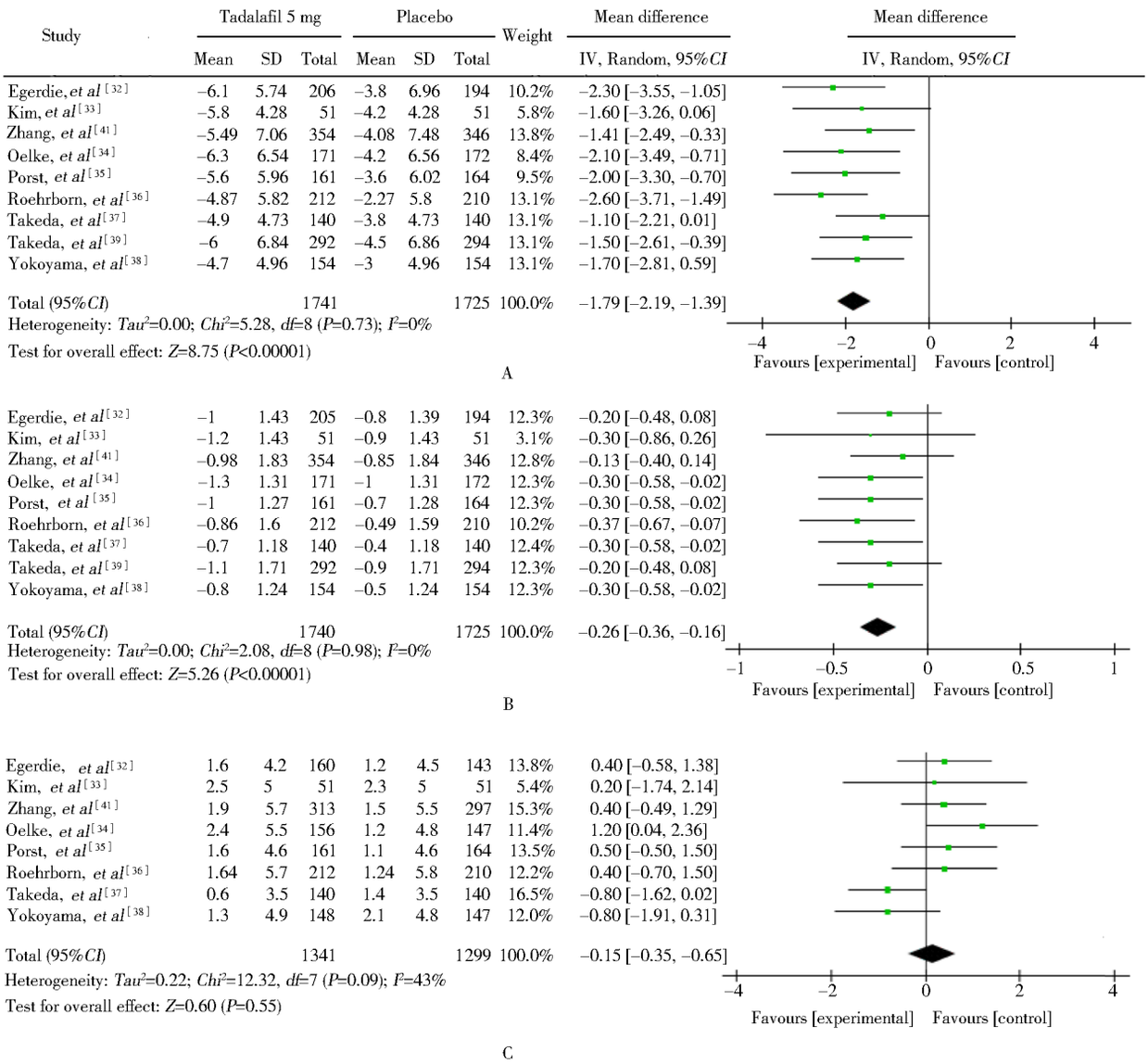


图 4 他达拉非 5 mg 组与安慰剂组荟萃分析森林图

Figure 4 Forest plots of meta-analysis between two groups

A: total IPSS; B: IPSS-Qol; C: Qmax. CI: confidence interval; IPSS: International Prostate Symptom Score; IPSS-Qol: IPSS quality of life; IV: inverse variance; Qmax: maximal urinary flow rate; SD: standard deviation.

表 2 GRADE 证据质量分级表

Table 2 GRADE level of evidence

Outcome indicator	Total sample (*n*)	Level of evidence (GRADE)
Total IPSS	3 466 (9 studies)	⊕⊕⊕⊕ high
IPSS-Qol	3 465 (9 studies)	⊕⊕⊕⊕ high
Qmax	2 640 (8 studies)	⊕ ΘΘΘ*,#,△ very low
Treatment withdrawal due to adverse events	3 523 (9 studies)	⊕⊕⊕ Θ△ moderate

GRADE: grading of recommendations assessment, development and evaluation; IPSS: International Prostate Symptom Score; IPSS-Qol: IPSS quality of life; Qmax: maximal urinary flow rate. *downgraded by one level for study limitations: unclear or high risk of bias for one or more domains among the included studies. #downgraded by two level for inconsistency: substantial heterogeneity among the included studies. △downgraded by one level for imprecision: confidence interval crosses assumed threshold of clinically important difference.

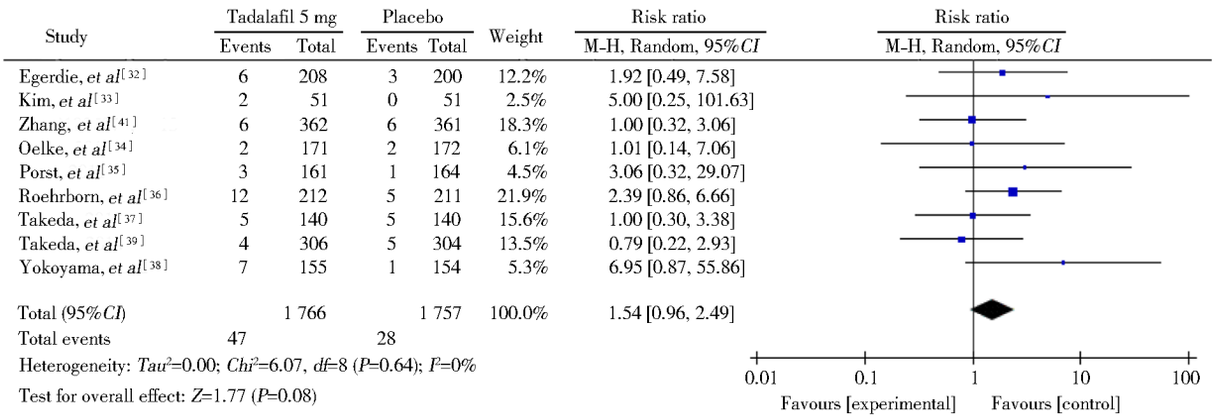


图5 2组中因发生不良事件退出研究患者比例的森林图

Figure 5 Forest plot in discontinuation due to adverse events in two groups

CI: confidence interval; M-H: Mantel-Haenszel.

表3 不良事件总结表

Table 3 Outcomes of treatment-emergent adverse events

TEAEs	*n*	*RR*	Lower limit	Upper limit	*P* value
Headache	47	1.59	0.99	2.56	0.06
Dyspepsia	31	7.31	2.57	20.81	<0.01
Back pain	29	2.04	1.03	4.07	0.04
Myalgia	15	5.91	1.53	22.82	0.01
Nasopharyngitis	52	1.04	0.70	1.54	0.84

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