Minimally invasive treatments for benign prostatic hyperplasia: a Cochrane network meta-analysis

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Complete List of Authors:	Franco, Juan Victor Ariel; Instituto Universitario del Hospital Italiano de Buenos Aires, Cochrane Center - Research Department; Hospital Italiano de Buenos Aires, Family and Community Medicine Division Jung, Jae Hung; Yonsei University Wonju College of Medicine, Urology Imamura, Mari; University of Aberdeen, Academic Urology Unit Borofsky, Michael S.; University of Minnesota, Department of Urology Omar, Muhammad Imran; University of Aberdeen, Academic Urology Unit; European Association of Urology, Guidelines Office Escobar Liquitay, Camila; Instituto Universitario del Hospital Italiano de Buenos Aires, Central Library Young, Shamar; University of Minnesota, Department of Radiology, Division of Interventional Radiology & Vascular Imaging Golzarian, Jafar; University of Minnesota, Department of Radiology, Division of Interventional Radiology & Vascular Imaging Veroniki, Areti Angeliki; University of Ioannina, Department of Primary Education, School of Education Garegnani, Luis; Instituto Universitario del Hospital Italiano de Buenos Aires, Cochrane Center - Research Department Dahm, Philipp; Urology Section 112D, Department of Veterans Affairs; Department of Urology, University of Minnesota
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Abstract:	Objective To assess the comparative effectiveness and ranking of minimally invasive treatments (MITs) for lower urinary tract symptoms (LUTS) in men with benign prostatic hyperplasia (BPH). Materials and methods We searched multiple databases up to 24 February 2021. We included randomized controlled trials assessing the following treatments: convective radiofrequency water vapour thermal therapy (WVTT or Rezum); prostatic arterial embolization (PAE); prostatic urethral lift (PUL or Urolift); temporary implantable nitinol device (TIND); and transurethral microwave thermotherapy (TUMT) compared to transurethral resection of the prostate (TURP) or sham surgery. We performed a frequentist network meta-analysis. Results

	We included 27 trials involving 3017 men. The overall certainty of the evidence of most outcomes according to GRADE was low to very low. Compared to TURP, PUL and PAE may result in little to no difference in urologic symptoms while WVTT, TUMT, and TIND may result in worse urologic symptoms. MITs may result in little to no difference in the quality of life (QoL), compared to TURP. MITs may result in a large reduction of major adverse events compared to TURP. We are uncertain about the effects of PAE and PUL on retreatment compared to TURP, however, TUMT may result in higher retreatment rates. We are very uncertain of the effects of MITs on erectile function and ejaculatory function. Among MITs, PUL and PAE have the highest likelihood of being the most efficacious for urinary symptoms and QoL, TUMT for major adverse events, WVTT and TIND for erectile function and PUL for ejaculatory function. Excluding WVTT and TIND, for which there were only studies with short-term (three months) follow-up, PUL had the highest likelihood of being the most efficacious for retreatment. Conclusions MITs may result in similar or worse effects concerning urinary symptoms and QoL compared to TURP at short-term follow-up.

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Authors
Juan VA Franco[1]
Jae Hung Jung[2,3]
Mari Imamura[4]
Michael Borofsky[5]
Muhammad Imran Omar[6,7]
Camila Micaela Escobar Liquitay[8]
Shamar Young[9]
Jafar Golzarian[9]
Areti Angeliki Veroniki[10]
Luis Garegnani[1]
Philipp Dahm[11]

1 - Associate Cochrane Centre, Instituto Universitario Hospital Italiano de Buenos Aires, Buenos Aires, Argentina
2 - Department of Urology, Yonsei University Wonju College of Medicine, Wonju, Korea, South
3 - Center of Evidence-Based Medicine, Institute of Convergence Science, Yonsei University, Seoul, Korea, South
4 - Health Services Research Unit, University of Aberdeen, Aberdeen, UK
5 - Department of Urology, University of Minnesota, Minneapolis, Minnesota, USA
6 - Guidelines Office, European Association of Urology, Arnhem, Netherlands
7 - Academic Urology Unit, University of Aberdeen, Aberdeen, UK
8 - Central Library, Instituto Universitario Hospital Italiano de Buenos Aires, Buenos Aires, Argentina
9 - Department of Radiology, Division of Interventional Radiology & Vascular Imaging, University of Minnesota, Minneapolis, Minnesota, USA
10 - Department of Primary Education, School of Education, University of Ioannina, Ioannina, Greece
11 - Urology Section, Minneapolis VA Health Care System, Minneapolis, Minnesota, USA

Corresponding author
Juan VA Franco
Associate Cochrane Centre
Instituto Universitario Hospital Italiano de Buenos Aires
Potosí 4234C1199ACL Buenos AiresBuenos Aires, Argentina
E-mail: juan.franco@hospitalitaliano.org.ar

Minimally invasive treatments for benign prostatic hyperplasia: a Cochrane network meta-analysis

Abstract

Objective
To assess the comparative effectiveness and ranking of minimally invasive treatments (MITs) for lower urinary tract symptoms (LUTS) in men with benign prostatic hyperplasia (BPH). **Materials and methods**
We searched multiple databases up to 24 February 2021. We included randomized controlled trials assessing the following treatments: convective radiofrequency water vapour thermal therapy (WVTT or Rezum); prostatic arterial embolization (PAE); prostatic urethral lift (PUL or Urolift); temporary implantable nitinol device (TIND); and transurethral microwave thermotherapy (TUMT) compared to transurethral resection of the prostate (TURP) or sham surgery. We performed a frequentist network meta-analysis.
Results
We included 27 trials involving 3017 men. The overall certainty of the evidence of most outcomes according to GRADE was low to very low. Compared to TURP, PUL and PAE may result in little to no difference in urologic symptoms while WVTT, TUMT, and TIND may result in worse urologic symptoms. MITs may result in little to no difference in the quality of life (QoL), compared to TURP. MITs may result in a large reduction of major adverse events compared to TURP. We are uncertain about the effects of PAE and PUL on retreatment compared to TURP, however, TUMT may result in higher retreatment rates. We are very uncertain of the effects of MITs on erectile function and ejaculatory function. Among MITs, PUL and PAE have the highest likelihood of being the most efficacious for urinary symptoms and QoL, TUMT for major adverse events, WVTT and TIND for erectile function and PUL for ejaculatory function. Excluding WVTT and TIND, for which there were only studies with short-term (three months) follow-up, PUL had the highest likelihood of being the most efficacious for retreatment.
Conclusions
MITs may result in similar or worse effects concerning urinary symptoms and QoL compared to TURP at short-term follow-up.

Keywords: benign prostatic hyperplasia, lower urinary tract symptoms, minimally invasive treatments, network meta-analysis, transurethral microwave thermotherapy; prostatic urethral lift, temporary implantable nitinol device, prostatic arterial embolisation.

Introduction

Benign prostatic obstruction is a form of bladder outlet obstruction and may be diagnosed when the cause of outlet obstruction is known to be benign prostatic hyperplasia (BPH)(1). BPH may or may not cause lower urinary tract symptoms (LUTS), characterised by urination frequency, hesitancy, and a weak stream, mainly in men over the age of 40, and receives clinical relevance when associated with perceived bother (2). Symptom bother typically correlates with increased number and severity of symptoms, which are related to impairment in the quality of life and treatment-seeking (3). Although we understand that LUTS is a functional unit with a multi-factorial aetiology of associated symptoms, we considered the term BPH for this Cochrane Review due to its familiarity with the general public(4). The degree of bother across all LUTS can be assessed through self-administered questionnaires, namely, the International Prostate Symptom Score (IPSS; also known as the American Urological Association [AUA] Symptom Index), which includes the quality of life domain(5). According to an international study involving 7588 men, the prevalence of LUTS was 18% during their 40s, 29% in their 50s, 40% in their 60s, and 56% in their 70s (6).
Initial treatment options for BPH include conservative management (watchful waiting and lifestyle modification) and the use of medications (alpha-blockers, 5-alpha reductase inhibitors, and, recently, phosphodiesterase inhibitors)(4). Surgical options are considered when patients have been refractory to conservative and medical treatment or if BPH causes subsequent complications, such as acute urinary retention, recurrent urinary tract infection, bladder stones, haematuria, or renal insufficiency (4). Clinical guidelines continue to recommend monopolar or bipolar transurethral resection of the prostate (TURP) as a ('gold') reference standard treatment to provide subjective symptom relief while attaining objective improvement in urinary flow (4,7), but this procedure is associated with some morbidity and long-term complications, including hematuria, possibly requiring a blood transfusion, urethral stricture, urinary tract infection, and incontinence, and it usually requires at least overnight hospitalisation. Moreover, men may experience ejaculatory (65%) and erectile dysfunction (10%) related to TURP(8). Furthermore, BPH is a common disease among elderly men, who have increased preoperative risk for complications of general anaesthesia and surgery in general(2). Recently, several other minimally invasive treatments (MITs) that can be performed in an office setting and do not require general anaesthesia have been developed as alternatives to TURP to provide therapeutic alternatives involving lower morbidity(4). However, given the relatively high rate of reoperation or continued use of medical therapy after surgical treatment (or both), concern has been raised about the durability of newly launched MIT(9).
MIT that can be performed in an office setting and do not require general anaesthesia and include: a) Convective radiofrequency water vapour therapy (WVTT or Rezum) which uses thermal energy in the form of water vapour to ablate prostatic tissue (10); b) Prostatic arterial embolisation (PAE) which uses super-selective micro catheterisation with microspheres to promote tissue necrosis(11); c) Prostatic urethral lift (PUL or Urolift) consists of separating and distracting enlarged prostatic tissue by a series of implants to hold excess prostatic tissue out of the way, thereby opening the narrowed urethra without cutting or removing enlarged prostatic tissue(12); d) Temporary implantable nitinol device (TIND) which involves 'reshaping' the prostatic urethra and bladder neck with an implantable device, thereby reducing urinary flow obstruction (13); and e) Transurethral microwave thermotherapy

(TUMT): which uses heat into the prostate via electromagnetic radiation of microwaves, inducing coagulation necrosis, reducing prostatic volume(14).

This review aims to assess the comparative effectiveness of minimally invasive treatments for lower urinary tract symptoms in men with benign prostatic hyperplasia and obtain an estimate of relative ranking. This is an abridged report of the full Cochrane review(15).

Materials and methods

Inclusion criteria

We followed standard Cochrane methods based on a published protocol(16). We included parallel-group randomised controlled trials (RCTs) including men > 40 years with a prostate volume of 20 mL or greater (as assessed by digital rectal examination, ultrasound, or cross-sectional imaging) with LUTS (determined by an IPSS of 8 or over), and a maximal urinary flow rate (Qmax) less than 15 mL/s (as measured by non-invasive uroflowmetry, invasive pressure flow studies, or both)(4). We excluded trials of men with other conditions that affect urinary symptoms. We included the following minimally invasive interventions defined as those that do not require general anaesthesia, compared to TURP or sham: WVTT, PAE, PUL, TIND and TUMT. We would also have included head-to-head comparisons between minimally invasive treatments, but none were found. We predefined the structure of the network and its nodes in our protocol (16). Participants in the network could in principle be randomised to any of the methods being compared, and we verified this by comparing characteristics of study design, participants, interventions, and comparisons while considering potential sources of clinical heterogeneity and effect modification (see Subgroup analysis and investigation of heterogeneity)(17).
Our main outcomes included urinary symptoms, quality of life, major adverse events, retreatment, erectile function and ejaculatory function. We considered clinically important differences for all outcomes as the basis for rating the certainty of the evidence for imprecision in the 'Summary of findings' table (18). We considered outcomes measured up to 12 months after randomisation as short-term and those later than 12 months as long-term, except for major adverse events (merging short and long-term data).

Search methods

We performed a comprehensive search with no restrictions on the language of publication or publication status. We retrieved relevant studies from existing Cochrane Reviews for each treatment (19–22). We updated searches for each of the individual Cochrane Reviews assessing each minimally invasive treatment. We performed a comprehensive search for TIND from the inception of each of the following databases until 24 February 2021: Cochrane Library via Wiley, MEDLINE via Ovid, Embase via Elsevier, Scopus, Web of Science, Latin American and the Caribbean Health Sciences Literature (LILACS) via Bireme, ClinicalTrials.gov at the US National Institutes of Health (www.clinicaltrials.gov/), World Health Organization (WHO) International Clinical Trials Registry Platform search portal (https://trialsearch.who.int/). We searched the reference lists of included studies, contacted experts, searched grey literature and screened abstract proceedings of relevant meetings.

Selection of studies

We used Covidence to identify and remove potential duplicate records(23). Two review authors (JVAF, LG) scanned abstracts, titles, or both to determine which studies should be assessed further using the same software, investigating all potentially relevant records as full text, and classified studies as included studies, excluded studies, studies awaiting classification, or ongoing studies following the criteria of the Cochrane Handbook(24). We resolved any discrepancies through consensus or recourse to a third review author (PD). We presented a PRISMA flow diagram showing the process of study selection(25).

Data extraction and risk of bias assessment

Because we retrieved relevant studies from existing Cochrane Reviews for each treatment for which study characteristics, outcome data, and risk of bias assessments were done by members of our review team (19–22), the following sections apply only to new studies identified by our search methods. For studies that fulfilled inclusion criteria, two review authors (of JVAF, LG, and JHJ) independently abstracted the characteristics of the participants, the interventions, comparisons and outcomes, funding sources and conflict of interests. We resolved any disagreements by discussion or, if required, by consultation with a third review author (PD). In addition, we contacted the authors of included studies to obtain key missing data as needed. Two review authors (JVAF and LG) independently assessed the risk of bias of each included study using the Cochrane tool for randomised controlled trials(26). We resolved disagreements by consensus or by consultation with a third review author (PD).

Statistical analysis and certainty of the evidence

We expressed dichotomous data as risk ratios (RRs) with 95% confidence interval (CIs) to enhance the interpretability of results. We expressed continuous data as mean differences (MDs) with 95% CIs. Before conducting a network meta-analysis, we assessed the transitivity assumption by visually inspecting the characteristics of the potential effect modifiers of the included studies across intervention comparisons (27). We evaluated the presence of inconsistency both locally by loop-specific method and globally by the design-by-treatment interaction model(28,29). We used comparison-adjusted funnel plots to assess small-study effects indicative of publication bias (30). We fitted a random-effects network meta-analysis model because we anticipated methodological and clinical heterogeneity across studies. We assumed a common within-network heterogeneity estimate across comparisons, and we estimated this using the restricted maximum likelihood (REML) method(31). We conducted a network meta-analysis using the network suite of commands in Stata (StataCorp. 2019) (29,32,33). We used the surface under the cumulative ranking curve (SUCRA) to rank the effectiveness and safety of minimally invasive interventions (34). When sufficient studies were available, we intended to perform subgroup analysis by age and severity of symptoms. We also planned to perform sensitivity analyses limited to the primary outcomes to explore the influence of risk of bias by excluding studies at 'high risk' or 'unclear risk'. We used 'Summary of findings' tables to summarise key results of the review, using the Confidence in Network Meta-analysis (CINeMA) framework and software (35,36). We presented an adapted single 'Summary of findings' table for all outcomes, using a modified approach based on the existent guidance (37).

Results

Search Results

We retrieved 26 studies from the previous Cochrane reviews. For the TIND search, we identified 469 records from electronic databases. After removing duplicates, we screened the titles and abstracts of the remaining 339 records, 331 of which we excluded. We assessed eight full-text articles, and we excluded six records for various reasons. Finally, we included one study (two reports) in this review for this intervention. We have shown the flow of literature through the assessment process in the PRISMA flowchart (**Figure 1**).

Characteristics of the Studies Included

We included 27 trials with 3017 randomised participants. Details of the included studies are presented in the Characteristics of included studies and **Table 1**. Most studies included men over 45 to 50 years old with moderate LUTS refractory to medical treatment; with a Qmax < 12/15 mL/s, a voided volume ≥ 125 mL and a prostate volume between 30/100 g to 60/100 g. Participants were usually screened for prostate cancer and infection, among other comorbidities, before inclusion. We included trials with the following interventions and comparisons: WVTT versus sham treatment (38), PAE versus sham treatment(39), PAE versus TURP (40–45), and PUL versus sham treatment (46), PUL versus TURP (47), TIND versus sham treatment (48), TUMT versus sham treatment (49–58), and TUMT versus TURP (59–64). Half of the studies did not state their funding sources, nine studies were funded by the manufacturers or sponsors of the procedure (38,39,43,46–48,55,57,64), and four were funded by public institutions or hospitals (40,49,56,63). All studies were considered at a high or unclear risk of bias, mainly due to lack of blinding in most comparisons, missing outcome data and poor reporting of the characteristics of the included studies. The details for the risk of bias and the characteristics of the excluded and ongoing studies can be found in the full version of the review(15).

Network meta-analysis: Minimally invasive treatments versus TURP

Considering that most trials assessed the effect of TUMT and PAE, the networks were not densely connected, and in some cases, they were star-shaped with no closed loops. The following analyses present data from networks with no concerns on transitivity or global consistency (except in those networks in which it was not possible to assess it due to the lack of closed loops). See **Table 2** for a summary of the main findings and **Figure 2** for a representation of the networks and their corresponding forest plot for each outcome.

Urologic symptoms scores

Based on 19 studies with 1847 participants PUL and PAE may result in little to no difference in urologic symptoms scores compared to TURP at short-term follow-up (3 to 12 months, MD of IPSS score, range 0 to 35, higher scores indicate worse symptoms; PUL: 1.47, 95% CI -4.00 to 6.93; PAE: 1.55, 95% CI -1.23 to 4.33). WVTT, TUMT, and TIND may result in worse urologic symptoms scores compared to TURP at short-term follow-up, but the confidence intervals include little to no difference (WVTT: 3.6, 95% CI -4.25 to 11.46; TUMT: 3.98, 95% CI 0.85 to 7.10; TIND: 7.5, 95% CI -0.68 to 15.69). TURP had the highest likelihood of being the most efficacious for this outcome; however, among minimally invasive procedures, PUL and PAE were the highest-ranked interventions. The certainty of the evidence is low due to major concerns about within-study bias, imprecision and inconsistency.

Quality of life

Based on 13 studies with 1469 participants, all interventions (PUL, PAE, WVTT, TUMT, TIND) may result in little to no difference in the quality of life scores compared to TURP at short-term follow-up (3 to 12 months; MD of IPSS-QoL score, range 0-6, higher scores indicate worse symptoms; PUL: 0.06, 95% CI -1.17 to 1.30; PAE: 0.09, 95% CI -0.57 to 0.75; WVTT: 0.37, 95% CI -1.45 to 2.20; TUMT: 0.65, 95% CI -0.48 to 1.78; TIND: 0.87, 95% CI -1.04 to 2.79). TURP had the highest likelihood of being the most efficacious for this outcome; however, among minimally invasive procedures, PUL and PAE were the highest-ranked interventions. The certainty of the evidence is low due to major concerns on within-study bias, imprecision and inconsistency.

Major adverse events

Based on 15 studies with 1573 participants, TUMT probably results in a large reduction in major adverse events compared to TURP (RR 0.20, 95% CI 0.09 to 0.43). PUL, WVTT, TIND, and PAE may also result in a large reduction in major adverse events, but the confidence interval includes substantial benefits and harms (at 3 to 36 months; PUL: RR 0.30, 95% CI 0.04 to 2.22; WVTT: RR 0.37, 95% CI 0.01 to 18.62; TIND: 0.52, 95% CI 0.01 to 24.46; PAE: 0.65, 95% CI 0.25 to 1.68). Furthermore, TUMT has the highest likelihood of being the most efficacious for this outcome, while TURP was the lowest-ranked intervention. The certainty of the evidence is low for WVTT, TIND, PUL, and PAE due to major concerns on the within-study bias and severe imprecision. The certainty of the evidence for TUMT is moderate due to major concerns on the within-study bias.

The most commonly reported major adverse events included hematuria with blood clots requiring evacuation or transfusion and severe infection. Less frequently and with a delayed presentation, some patients developed meatal/urethral stenosis, which usually required additional procedures for resolution (bladder neck incision/urethrotomy).

Retreatment

Based on ten studies with 799 participants, we are uncertain about the effects of PAE and PUL on retreatment compared to TURP at long-term follow-up (12 to 60 months; PUL: RR 2.39, 95% CI 0.51 to 11.1; PAE: RR 4.39, 95% CI 1.25 to 15.44). TUMT may result in a higher increase in retreatment rates (RR 9.71, 95% CI 2.35 to 40.13). TURP had the highest likelihood of being the most efficacious for this outcome; however, PUL was the highest-

ranked intervention among minimally invasive procedures. The certainty of the evidence is very low for PUL and PAE due to major concerns about the within-study bias, imprecision, inconsistency and incoherence. The certainty of the evidence for TUMT is low due to major concerns about within-study bias and incoherence.
These results do not include WVTT or TIND because of short-term follow-up (these results are displayed separately below, under pairwise comparisons).

Erectile function

Based on six studies with 640 participants (Abt 2018; Carnevale 2016; Chughtai 2020; Gratzke 2017; McVary 2016; Roehrborn 2013), we are very uncertain of the effects of minimally invasive treatments on erectile function (MD of IIEF-5, range 5 to 25, higher scores indicates better function; WVTT: 6.49, 95% CI -8.13 to 21.12; TIND: 5.19, 95% CI -9.36 to 19.74; PUL: 3.00, 95% CI -5.45 to 11.44; PAE: -0.03, 95% CI -6.38, 6.32). WVTT and TIND have the highest likelihood of being the most efficacious for this outcome, while TURP was the lowest-ranked intervention; the certainty of the evidence is very low due to major concerns about the within-study bias, incoherence and severe imprecision.
Studies related to TUMT did not report this outcome as defined in this analysis (these results are displayed separately below in pairwise comparisons).

Ejaculatory function

Based on eight studies with 461 participants, we are uncertain of the effects of PUL, PAE, and TUMT on ejaculatory dysfunction compared to TURP (at 3 to 12 months; PUL: RR 0.05, 95 % CI 0.00 to 1.06; PAE: RR 0.35, 95% CI 0.13 to 0.92; TUMT: RR 0.34, 95% CI 0.17 to 0.68). PUL has the highest likelihood of being the most efficacious for this outcome, while TURP was the lowest-ranked intervention. The certainty of the evidence is very low due to major concerns about the within-study bias, inconsistency, and incoherence.
WVTT was not included in this section because these studies were disconnected from the network (see description below). In addition, the study assessing TIND reported no events of ejaculatory dysfunction.

Pairwise comparisons

We describe here some key information that we were unable to include in our network meta-analysis to preserve the transitivity of each network.

Retreatment: WVTT and TIND

Based on one study with 197 participants, we are uncertain about the effects of WVTT on retreatment compared to sham treatment at three months follow-up (RR 1.36, 95% CI 0.06 to 32.86)(38). Based on another study with 185 participants, we are very uncertain about the effects of TIND on retreatment compared to sham treatment at three-month follow-up (RR 0.67, 95% CI 0.11 to 3.89)(48). The certainty of the evidence is very low due to concerns about the risk of bias and severe imprecision. These results could not be included in the network due to their short-term follow-up.

Erectile function: TUMT

Based on four studies with 278 participants, TUMT may result in little to no difference in erectile function (defined as an event of erectile dysfunction) compared to TURP at short-term follow-up (RR 0.79, 95% CI 0.40 to 1.55; $I^2 = 0\%$). One study found a similar result at long-term follow-up (RR 0.49, 95% CI 0.17 to 1.41)(64). However, the certainty of the evidence is low due to concerns about the risk of bias and imprecision. These results could not be included in the network because they were assessed as binary data and not IIEF scores.

Ejaculatory function: WVTT

Based on one study with 131 participants, WVTT may result in little to no difference in events of ejaculatory dysfunction compared to sham treatment at short-term follow-up (RR 4.01, 95% CI 0.22 to 72.78)(38). The certainty of the evidence is low due to concerns about the risk of bias and imprecision. These results could not be included in the network because they were disconnected from all nodes.

Subgroup analysis

We found no subgroup differences in urologic symptoms scores according to age or symptom severity. We found no subgroup differences in quality of life according to age. Most of the prespecified subgroup analyses were not possible to perform due to the scarcity of data.

Discussion

We included 27 trials with 3017 randomised participants, assessing the effects of minimally invasive treatments compared to TURP or sham treatment. TURP is the reference treatment and was found to have the highest likelihood of being the most efficacious for urinary symptoms, quality of life, retreatment, minor adverse events, and acute urinary retention, but the least favourable in terms of major adverse events, erectile function, and ejaculatory function. Among minimally invasive procedures, PUL and PAE have the highest likelihood of being the most efficacious for urinary symptoms and quality of life; TUMT for major adverse events; PUL for retreatment, ejaculatory function, and acute urinary retention; WVTT and TIND for erectile function; and PAE for minor adverse events.

The largest limitation of this study relates to issues related to the underlying body of evidence (see below), particularly the lack of head-to-head trials for MITs against TURP. For example, RCTs for WVTT and TIND were limited to comparisons against sham treatment that were unblinded after three months and had a short-term follow-up in many cases. The latter issues are underscored by the fact that the AUA guideline panel on the surgical management of LUTS had determined it required a minimum follow-up of greater than 12 months to support its recommendations(65,66). Since longer-term RCT data is so limited, observational data may provide complementary information. For example, a systematic review of such studies found that the retreatment rate may be higher for PUL than assessed here, close to 6% per year(67). Meanwhile, another systematic review has suggested that the long-term effects of WVTT may be sustained with a relatively low retreatment rate(68).

The reporting of adverse events was not uniform across studies, especially those different across procedures, such as the 'post-embolization syndrome' in PAE. This was also highlighted in a recent review of observational data in which over a quarter of patients suffered this syndrome, but it was not uniformly characterised (69). Whereas the Clavien-Dindo system provides a well-established system to grade the severity of surgical complications, it may be less than ideal to characterise, for example, the adverse event profile for such different MITs as PUL and PAE.

A recent systematic review on men's values and preferences highlighted that they expect a high success rate with low remission and complication rates, which minimally invasive treatments may provide compared to TURP (70). However, men also value the preservation of their sexual function, for which we have greater uncertainties. Therefore, clinicians must engage in shared-decision making with their patients when discussing the available options(71).

The certainty of the evidence was mostly low to very low due to the risk of bias, imprecision, inconsistency and the inability to assess incoherence in loosely connected networks. There is also the possibility of novelty bias, which refers to the mere appearance that a new treatment is better when it is new(27,72). We made minor modifications from our protocol regarding the reporting of additional data available in each supporting review and the display of the ranking results both graphically and in the 'Summary of findings' tables. All these changes were duly documented in the full version of the review(15). We could not include all available trials and interventions in all networks, primarily due to the lack of reporting of the outcomes in the desired format or definition. Finally, we could not perform subgroup and sensibility analysis due to the limited representation of subgroups in trials. Moreover, sensitivity analyses were not possible, considering that most of the studies were at a high or unclear risk of bias.

We identified several systematic reviews focusing on minimally invasive treatments, reporting similar findings concerning the efficacy of TIND, PUL, PAE, and WVTT, and highlighting that these are relatively effective treatments, with a lower incidence of adverse events and sexual dysfunction, compared to TURP (73–78). While some of these findings are similar to our review, we highlight the uncertainty surrounding some of these outcomes, especially those related to sexual function, in which the data are sparse and usually available for only a subset of participants in each study, as was highlighted by one review (79). Furthermore, many of these reviews included evidence from non-randomized studies and had an overall low quality(80,81). In some cases, the evidence was synthesised by the authors of the primary studies (73). Finally, there is a paucity of reviews focusing on TUMT in the last few years, considering that no trials are available since the previous version of the Cochrane Review(82).

Conclusions

Minimally invasive treatments may result in similar or worse effects concerning urinary symptoms and quality of life, compared to the standard treatment (transurethral resection of the prostate) at short-term follow-up. They may result in a large reduction of major adverse events, especially in the use of prostatic urethral lift and prostatic arterial embolisation, which resulted in better rankings for symptomatic symptoms scores. Prostatic urethral lift may result in fewer retreatments than other interventions, especially transurethral microwave

thermotherapy, which has the highest retreatment rates at long-term follow-up. We are very uncertain about the effects of these interventions on erectile function; however, these treatments may result in fewer cases of ejaculatory dysfunction. Considering that patients value the effects of these treatments on urinary symptoms, retreatment rates, and adverse events, including sexual function, it becomes necessary to engage in shared decision-making when discussing their different treatment options, highlighting the existing uncertainties and eliciting their preferences.

There needs to be better reporting of basic trial methodology and a greater emphasis on patient-reported outcomes, especially those related to sexual function. Many studies broke the blinding period after three months, and patients crossed to the active treatment group, which prevented us from knowing the long-term effects of these interventions. This is particularly relevant for convective radiofrequency water vapour therapy and temporary implantable nitinol device, both of which are supported only by single trials that compared the new therapeutic approach to sham control, with a three-month time horizon. Sham-controlled trials provide only limited and indirect evidence to inform decision-making, and future research could focus on active comparisons and patient-important outcomes with a follow up greater than 12 months (65,66,83). A core outcome set should establish which outcomes should be collected and how and when they should be collected.

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Contributions of authors

JVAF: conception and study design and drafting the protocol, data extraction and analysis, writing the full review. JHJ: drafting the protocol, data extraction and analysis, writing the full review. MI: drafting the protocol, providing clinical input and approving the final draft. MB: drafting the protocol, providing clinical input and approving the final draft. SY: revising the protocol, providing clinical input and approving the final draft. MIO: drafting the protocol, providing clinical input and approving the final draft. JG: providing clinical input and approving the final draft. CMEL: creating search strategies and searching for trials, writing the methods and results section related to the searches and approving the final draft. AAV: drafting the protocol, providing supervision on the statistics and approving the final draft. LG: drafting the protocol, data extraction and analysis, writing the full review. PD: conception and study design, providing clinical and methodological advice on the protocol.

Disclosure of Interests

JVAF, JHJ, MI, JG, MIO, CMEL, AAV, LG, and PD: none known. SY: Boston Scientific (speaker), Galvanize (consultant). MB: Boston Scientific (consultant for endourology and stone management), Auris Health (consultant for robotic surgery and endourology), Urotronic (disease monitoring and safety board).

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Minimally invasive treatments for benign prostatic hyperplasia: a Cochrane network meta-analysis

Abstract

Objective

To assess the comparative effectiveness and ranking of minimally invasive treatments (MITs) for lower urinary tract symptoms (LUTS) in men with benign prostatic hyperplasia (BPH).

Materials and methods

We searched multiple databases up to 24 February 2021. We included randomized controlled trials assessing the following treatments: convective radiofrequency water vapour thermal therapy (WVTT or Rezum); prostatic arterial embolization (PAE); prostatic urethral lift (PUL or Urolift); temporary implantable nitinol device (TIND); and transurethral microwave thermotherapy (TUMT) compared to transurethral resection of the prostate (TURP) or sham surgery. We performed a frequentist network meta-analysis.

Results

We included 27 trials involving 3017 men. The overall certainty of the evidence of most outcomes according to GRADE was low to very low. Compared to TURP, PUL and PAE may result in little to no difference in urologic symptoms while WVTT, TUMT, and TIND may result in worse urologic symptoms. MITs may result in little to no difference in the quality of life (QoL), compared to TURP. MITs may result in a large reduction of major adverse events compared to TURP. We are uncertain about the effects of PAE and PUL on retreatment compared to TURP, however, TUMT may result in higher retreatment rates. We are very uncertain of the effects of MITs on erectile function and ejaculatory function. Among MITs, PUL and PAE have the highest likelihood of being the most efficacious for urinary symptoms and QoL, TUMT for major adverse events, WVTT and TIND for erectile function and PUL for ejaculatory function. Excluding WVTT and TIND, for which there were only studies with short-term (three months) follow-up, PUL had the highest likelihood of being the most efficacious for retreatment.

Conclusions

MITs may result in similar or worse effects concerning urinary symptoms and QoL compared to TURP at short-term follow-up.

Keywords: benign prostatic hyperplasia, lower urinary tract symptoms, minimally invasive treatments, network meta-analysis, transurethral microwave thermotherapy; prostatic urethral lift, temporary implantable nitinol device, prostatic arterial embolisation.

Introduction

Benign prostatic obstruction is a form of bladder outlet obstruction and may be diagnosed when the cause of outlet obstruction is known to be benign prostatic hyperplasia (BPH)(1). BPH may or may not cause lower urinary tract symptoms (LUTS), characterised by urination frequency, hesitancy, and a weak stream, mainly in men over the age of 40, and receives clinical relevance when associated with perceived bother (2). Symptom bother typically correlates with increased number and severity of symptoms, which are related to impairment in the quality of life and treatment-seeking (3). Although we understand that LUTS is a functional unit with a multi-factorial aetiology of associated symptoms, we considered the term BPH for this Cochrane Review due to its familiarity with the general public(4). The degree of bother across all LUTS can be assessed through self-administered questionnaires, namely, the International Prostate Symptom Score (IPSS; also known as the American Urological Association [AUA] Symptom Index), which includes the quality of life domain(5). According to an international study involving 7588 men, the prevalence of LUTS was 18% during their 40s, 29% in their 50s, 40% in their 60s, and 56% in their 70s (6).
Initial treatment options for BPH include conservative management (watchful waiting and lifestyle modification) and the use of medications (alpha-blockers, 5-alpha reductase inhibitors, and, recently, phosphodiesterase inhibitors)(4). Surgical options are considered when patients have been refractory to conservative and medical treatment or if BPH causes subsequent complications, such as acute urinary retention, recurrent urinary tract infection, bladder stones, haematuria, or renal insufficiency (4). Clinical guidelines continue to recommend monopolar or bipolar transurethral resection of the prostate (TURP) as a ('gold') reference standard treatment to provide subjective symptom relief while attaining objective improvement in urinary flow (4,7), but this procedure is associated with some morbidity and long-term complications, including hematuria, possibly requiring a blood transfusion, urethral stricture, urinary tract infection, and incontinence, and it usually requires at least overnight hospitalisation. Moreover, men may experience ejaculatory (65%) and erectile dysfunction (10%) related to TURP(8). Furthermore, BPH is a common disease among elderly men, who have increased preoperative risk for complications of general anaesthesia and surgery in general(2). Recently, several other minimally invasive treatments (MITs) that can be performed in an office setting and do not require general anaesthesia have been developed as alternatives to TURP to provide therapeutic alternatives involving lower morbidity(4). However, given the relatively high rate of reoperation or continued use of medical therapy after surgical treatment (or both), concern has been raised about the durability of newly launched MIT(9).
MIT that can be performed in an office setting and do not require general anaesthesia and include: a) Convective radiofrequency water vapour therapy (WVTT or Rezum) which uses thermal energy in the form of water vapour to ablate prostatic tissue (10); b) Prostatic arterial embolisation (PAE) which uses super-selective micro catheterisation with microspheres to promote tissue necrosis(11); c) Prostatic urethral lift (PUL or Urolift) consists of separating and distracting enlarged prostatic tissue by a series of implants to hold excess prostatic tissue out of the way, thereby opening the narrowed urethra without cutting or removing enlarged prostatic tissue(12); d) Temporary implantable nitinol device (TIND) which involves 'reshaping' the prostatic urethra and bladder neck with an implantable device, thereby reducing urinary flow obstruction (13); and e) Transurethral microwave thermotherapy

(TUMT): which uses heat into the prostate via electromagnetic radiation of microwaves, inducing coagulation necrosis, reducing prostatic volume(14).

This review aims to assess the comparative effectiveness of minimally invasive treatments for lower urinary tract symptoms in men with benign prostatic hyperplasia and obtain an estimate of relative ranking. This is an abridged report of the full Cochrane review(15).

Materials and methods

Inclusion criteria

We followed standard Cochrane methods based on a published protocol(16). We included parallel-group randomised controlled trials (RCTs) including men > 40 years with a prostate volume of 20 mL or greater (as assessed by digital rectal examination, ultrasound, or cross-sectional imaging) with LUTS (determined by an IPSS of 8 or over), and a maximal urinary flow rate (Qmax) less than 15 mL/s (as measured by non-invasive uroflowmetry, invasive pressure flow studies, or both)(4). We excluded trials of men with other conditions that affect urinary symptoms. We included the following minimally invasive interventions defined as those that do not require general anaesthesia, compared to TURP or sham: WVTT, PAE, PUL, TIND and TUMT. We would also have included head-to-head comparisons between minimally invasive treatments, but none were found. We predefined the structure of the network and its nodes in our protocol (16). Participants in the network could in principle be randomised to any of the methods being compared, and we verified this by comparing characteristics of study design, participants, interventions, and comparisons while considering potential sources of clinical heterogeneity and effect modification (see Subgroup analysis and investigation of heterogeneity)(17).
Our main outcomes included urinary symptoms, quality of life, major adverse events, retreatment, erectile function and ejaculatory function. We considered clinically important differences for all outcomes as the basis for rating the certainty of the evidence for imprecision in the 'Summary of findings' table (18). We considered outcomes measured up to 12 months after randomisation as short-term and those later than 12 months as long-term, except for major adverse events (merging short and long-term data).

Search methods

We performed a comprehensive search with no restrictions on the language of publication or publication status. We retrieved relevant studies from existing Cochrane Reviews for each treatment (19–22). We updated searches for each of the individual Cochrane Reviews assessing each minimally invasive treatment. We performed a comprehensive search for TIND from the inception of each of the following databases until 24 February 2021: Cochrane Library via Wiley, MEDLINE via Ovid, Embase via Elsevier, Scopus, Web of Science, Latin American and the Caribbean Health Sciences Literature (LILACS) via Bireme, ClinicalTrials.gov at the US National Institutes of Health (www.clinicaltrials.gov/), World Health Organization (WHO) International Clinical Trials Registry Platform search portal (https://trialsearch.who.int/). We searched the reference lists of included studies, contacted experts, searched grey literature and screened abstract proceedings of relevant meetings.

Selection of studies

We used Covidence to identify and remove potential duplicate records(23). Two review authors (JVAF, LG) scanned abstracts, titles, or both to determine which studies should be assessed further using the same software, investigating all potentially relevant records as full text, and classified studies as included studies, excluded studies, studies awaiting classification, or ongoing studies following the criteria of the Cochrane Handbook(24). We resolved any discrepancies through consensus or recourse to a third review author (PD). We presented a PRISMA flow diagram showing the process of study selection(25).

Data extraction and risk of bias assessment

Because we retrieved relevant studies from existing Cochrane Reviews for each treatment for which study characteristics, outcome data, and risk of bias assessments were done by members of our review team (19–22), the following sections apply only to new studies identified by our search methods. For studies that fulfilled inclusion criteria, two review authors (of JVAF, LG, and JHJ) independently abstracted the characteristics of the participants, the interventions, comparisons and outcomes, funding sources and conflict of interests. We resolved any disagreements by discussion or, if required, by consultation with a third review author (PD). In addition, we contacted the authors of included studies to obtain key missing data as needed. Two review authors (JVAF and LG) independently assessed the risk of bias of each included study using the Cochrane tool for randomised controlled trials(26). We resolved disagreements by consensus or by consultation with a third review author (PD).

Statistical analysis and certainty of the evidence

We expressed dichotomous data as risk ratios (RRs) with 95% confidence interval (CIs) to enhance the interpretability of results. We expressed continuous data as mean differences (MDs) with 95% CIs. Before conducting a network meta-analysis, we assessed the transitivity assumption by visually inspecting the characteristics of the potential effect modifiers of the included studies across intervention comparisons (27). We evaluated the presence of inconsistency both locally by loop-specific method and globally by the design-by-treatment interaction model(28,29). We used comparison-adjusted funnel plots to assess small-study effects indicative of publication bias (30). We fitted a random-effects network meta-analysis model because we anticipated methodological and clinical heterogeneity across studies. We assumed a common within-network heterogeneity estimate across comparisons, and we estimated this using the restricted maximum likelihood (REML) method(31). We conducted a network meta-analysis using the network suite of commands in Stata (StataCorp. 2019) (29,32,33). We used the surface under the cumulative ranking curve (SUCRA) to rank the effectiveness and safety of minimally invasive interventions (34). When sufficient studies were available, we intended to perform subgroup analysis by age and severity of symptoms. We also planned to perform sensitivity analyses limited to the primary outcomes to explore the influence of risk of bias by excluding studies at 'high risk' or 'unclear risk'. We used 'Summary of findings' tables to summarise key results of the review, using the Confidence in Network Meta-analysis (CINeMA) framework and software (35,36). We presented an adapted single 'Summary of findings' table for all outcomes, using a modified approach based on the existent guidance (37).

Results

Search Results

We retrieved 26 studies from the previous Cochrane reviews. For the TIND search, we identified 469 records from electronic databases. After removing duplicates, we screened the titles and abstracts of the remaining 339 records, 331 of which we excluded. We assessed eight full-text articles, and we excluded six records for various reasons. Finally, we included one study (two reports) in this review for this intervention. We have shown the flow of literature through the assessment process in the PRISMA flowchart (**Figure 1**).

Characteristics of the Studies Included

We included 27 trials with 3017 randomised participants. Details of the included studies are presented in the Characteristics of included studies and **Table 1**. Most studies included men over 45 to 50 years old with moderate LUTS refractory to medical treatment; with a Qmax < 12/15 mL/s, a voided volume ≥ 125 mL and a prostate volume between 30/100 g to 60/100 g. Participants were usually screened for prostate cancer and infection, among other comorbidities, before inclusion. We included trials with the following interventions and comparisons: WVTT versus sham treatment (38), PAE versus sham treatment(39), PAE versus TURP (40–45), and PUL versus sham treatment (46), PUL versus TURP (47), TIND versus sham treatment (48), TUMT versus sham treatment (49–58), and TUMT versus TURP (59–64). Half of the studies did not state their funding sources, nine studies were funded by the manufacturers or sponsors of the procedure (38,39,43,46–48,55,57,64), and four were funded by public institutions or hospitals (40,49,56,63). All studies were considered at a high or unclear risk of bias, mainly due to lack of blinding in most comparisons, missing outcome data and poor reporting of the characteristics of the included studies. The details for the risk of bias and the characteristics of the excluded and ongoing studies can be found in the full version of the review(15).

Network meta-analysis: Minimally invasive treatments versus TURP

Considering that most trials assessed the effect of TUMT and PAE, the networks were not densely connected, and in some cases, they were star-shaped with no closed loops. The following analyses present data from networks with no concerns on transitivity or global consistency (except in those networks in which it was not possible to assess it due to the lack of closed loops). See **Table 2** for a summary of the main findings and **Figure 2** for a representation of the networks and their corresponding forest plot for each outcome.

Urologic symptoms scores

Based on 19 studies with 1847 participants PUL and PAE may result in little to no difference in urologic symptoms scores compared to TURP at short-term follow-up (3 to 12 months, MD of IPSS score, range 0 to 35, higher scores indicate worse symptoms; PUL: 1.47, 95% CI -4.00 to 6.93; PAE: 1.55, 95% CI -1.23 to 4.33). WVTT, TUMT, and TIND may result in worse urologic symptoms scores compared to TURP at short-term follow-up, but the confidence intervals include little to no difference (WVTT: 3.6, 95% CI -4.25 to 11.46; TUMT: 3.98, 95% CI 0.85 to 7.10; TIND: 7.5, 95% CI -0.68 to 15.69). TURP had the highest likelihood of being the most efficacious for this outcome; however, among minimally invasive procedures, PUL and PAE were the highest-ranked interventions. The certainty of the evidence is low due to major concerns about within-study bias, imprecision and inconsistency.

Quality of life

Based on 13 studies with 1469 participants, all interventions (PUL, PAE, WVTT, TUMT, TIND) may result in little to no difference in the quality of life scores compared to TURP at short-term follow-up (3 to 12 months; MD of IPSS-QoL score, range 0-6, higher scores indicate worse symptoms; PUL: 0.06, 95% CI -1.17 to 1.30; PAE: 0.09, 95% CI -0.57 to 0.75; WVTT: 0.37, 95% CI -1.45 to 2.20; TUMT: 0.65, 95% CI -0.48 to 1.78; TIND: 0.87, 95% CI -1.04 to 2.79). TURP had the highest likelihood of being the most efficacious for this outcome; however, among minimally invasive procedures, PUL and PAE were the highest-ranked interventions. The certainty of the evidence is low due to major concerns on within-study bias, imprecision and inconsistency.

Major adverse events

Based on 15 studies with 1573 participants, TUMT probably results in a large reduction in major adverse events compared to TURP (RR 0.20, 95% CI 0.09 to 0.43). PUL, WVTT, TIND, and PAE may also result in a large reduction in major adverse events, but the confidence interval includes substantial benefits and harms (at 3 to 36 months; PUL: RR 0.30, 95% CI 0.04 to 2.22; WVTT: RR 0.37, 95% CI 0.01 to 18.62; TIND: 0.52, 95% CI 0.01 to 24.46; PAE: 0.65, 95% CI 0.25 to 1.68). Furthermore, TUMT has the highest likelihood of being the most efficacious for this outcome, while TURP was the lowest-ranked intervention. The certainty of the evidence is low for WVTT, TIND, PUL, and PAE due to major concerns on the within-study bias and severe imprecision. The certainty of the evidence for TUMT is moderate due to major concerns on the within-study bias.

The most commonly reported major adverse events included hematuria with blood clots requiring evacuation or transfusion and severe infection. Less frequently and with a delayed presentation, some patients developed meatal/urethral stenosis, which usually required additional procedures for resolution (bladder neck incision/urethrotomy).

Retreatment

Based on ten studies with 799 participants, we are uncertain about the effects of PAE and PUL on retreatment compared to TURP at long-term follow-up (12 to 60 months; PUL: RR 2.39, 95% CI 0.51 to 11.1; PAE: RR 4.39, 95% CI 1.25 to 15.44). TUMT may result in a higher increase in retreatment rates (RR 9.71, 95% CI 2.35 to 40.13). TURP had the highest likelihood of being the most efficacious for this outcome; however, PUL was the highest-

ranked intervention among minimally invasive procedures. The certainty of the evidence is very low for PUL and PAE due to major concerns about the within-study bias, imprecision, inconsistency and incoherence. The certainty of the evidence for TUMT is low due to major concerns about within-study bias and incoherence.
These results do not include WVTT or TIND because of short-term follow-up (these results are displayed separately below, under pairwise comparisons).

Erectile function

Based on six studies with 640 participants (Abt 2018; Carnevale 2016; Chughtai 2020; Gratzke 2017; McVary 2016; Roehrborn 2013), we are very uncertain of the effects of minimally invasive treatments on erectile function (MD of IIEF-5, range 5 to 25, higher scores indicates better function; WVTT: 6.49, 95% CI -8.13 to 21.12; TIND: 5.19, 95% CI -9.36 to 19.74; PUL: 3.00, 95% CI -5.45 to 11.44; PAE: -0.03, 95% CI -6.38, 6.32). WVTT and TIND have the highest likelihood of being the most efficacious for this outcome, while TURP was the lowest-ranked intervention; the certainty of the evidence is very low due to major concerns about the within-study bias, incoherence and severe imprecision.
Studies related to TUMT did not report this outcome as defined in this analysis (these results are displayed separately below in pairwise comparisons).

Ejaculatory function

Based on eight studies with 461 participants, we are uncertain of the effects of PUL, PAE, and TUMT on ejaculatory dysfunction compared to TURP (at 3 to 12 months; PUL: RR 0.05, 95 % CI 0.00 to 1.06; PAE: RR 0.35, 95% CI 0.13 to 0.92; TUMT: RR 0.34, 95% CI 0.17 to 0.68). PUL has the highest likelihood of being the most efficacious for this outcome, while TURP was the lowest-ranked intervention. The certainty of the evidence is very low due to major concerns about the within-study bias, inconsistency, and incoherence.
WVTT was not included in this section because these studies were disconnected from the network (see description below). In addition, the study assessing TIND reported no events of ejaculatory dysfunction.

Pairwise comparisons

We describe here some key information that we were unable to include in our network meta-analysis to preserve the transitivity of each network.

Retreatment: WVTT and TIND

Based on one study with 197 participants, we are uncertain about the effects of WVTT on retreatment compared to sham treatment at three months follow-up (RR 1.36, 95% CI 0.06 to 32.86)(38). Based on another study with 185 participants, we are very uncertain about the effects of TIND on retreatment compared to sham treatment at three-month follow-up (RR 0.67, 95% CI 0.11 to 3.89)(48). The certainty of the evidence is very low due to concerns about the risk of bias and severe imprecision. These results could not be included in the network due to their short-term follow-up.

Erectile function: TUMT

Based on four studies with 278 participants, TUMT may result in little to no difference in erectile function (defined as an event of erectile dysfunction) compared to TURP at short-term follow-up (RR 0.79, 95% CI 0.40 to 1.55; $I^2 = 0\%$). One study found a similar result at long-term follow-up (RR 0.49, 95% CI 0.17 to 1.41)(64). However, the certainty of the evidence is low due to concerns about the risk of bias and imprecision. These results could not be included in the network because they were assessed as binary data and not IIEF scores.

Ejaculatory function: WVTT

Based on one study with 131 participants, WVTT may result in little to no difference in events of ejaculatory dysfunction compared to sham treatment at short-term follow-up (RR 4.01, 95% CI 0.22 to 72.78)(38). The certainty of the evidence is low due to concerns about the risk of bias and imprecision. These results could not be included in the network because they were disconnected from all nodes.

Subgroup analysis

We found no subgroup differences in urologic symptoms scores according to age or symptom severity. We found no subgroup differences in quality of life according to age. Most of the prespecified subgroup analyses were not possible to perform due to the scarcity of data.

Discussion

We included 27 trials with 3017 randomised participants, assessing the effects of minimally invasive treatments compared to TURP or sham treatment. TURP is the reference treatment and was found to have the highest likelihood of being the most efficacious for urinary symptoms, quality of life, retreatment, minor adverse events, and acute urinary retention, but the least favourable in terms of major adverse events, erectile function, and ejaculatory function. Among minimally invasive procedures, PUL and PAE have the highest likelihood of being the most efficacious for urinary symptoms and quality of life; TUMT for major adverse events; PUL for retreatment, ejaculatory function, and acute urinary retention; WVTT and TIND for erectile function; and PAE for minor adverse events.

The largest limitation of this study relates to issues related to the underlying body of evidence (see below), particularly the lack of head-to-head trials for MITs against TURP. For example, RCTs for WVTT and TIND were limited to comparisons against sham treatment that were unblinded after three months and had a short-term follow-up in many cases. The latter issues are underscored by the fact that the AUA guideline panel on the surgical management of LUTS had determined it required a minimum follow-up of greater than 12 months to support its recommendations(65,66). Since longer-term RCT data is so limited, observational data may provide complementary information. For example, a systematic review of such studies found that the retreatment rate may be higher for PUL than assessed here, close to 6% per year(67). Meanwhile, another systematic review has suggested that the long-term effects of WVTT may be sustained with a relatively low retreatment rate(68).

The reporting of adverse events was not uniform across studies, especially those different across procedures, such as the 'post-embolization syndrome' in PAE. This was also highlighted in a recent review of observational data in which over a quarter of patients suffered this syndrome, but it was not uniformly characterised (69). Whereas the Clavien-Dindo system provides a well-established system to grade the severity of surgical complications, it may be less than ideal to characterise, for example, the adverse event profile for such different MITs as PUL and PAE.

A recent systematic review on men's values and preferences highlighted that they expect a high success rate with low remission and complication rates, which minimally invasive treatments may provide compared to TURP (70). However, men also value the preservation of their sexual function, for which we have greater uncertainties. Therefore, clinicians must engage in shared-decision making with their patients when discussing the available options(71).

The certainty of the evidence was mostly low to very low due to the risk of bias, imprecision, inconsistency and the inability to assess incoherence in loosely connected networks. There is also the possibility of novelty bias, which refers to the mere appearance that a new treatment is better when it is new(27,72). We made minor modifications from our protocol regarding the reporting of additional data available in each supporting review and the display of the ranking results both graphically and in the 'Summary of findings' tables. All these changes were duly documented in the full version of the review(15). We could not include all available trials and interventions in all networks, primarily due to the lack of reporting of the outcomes in the desired format or definition. Finally, we could not perform subgroup and sensibility analysis due to the limited representation of subgroups in trials. Moreover, sensitivity analyses were not possible, considering that most of the studies were at a high or unclear risk of bias.

We identified several systematic reviews focusing on minimally invasive treatments, reporting similar findings concerning the efficacy of TIND, PUL, PAE, and WVTT, and highlighting that these are relatively effective treatments, with a lower incidence of adverse events and sexual dysfunction, compared to TURP (73–78). While some of these findings are similar to our review, we highlight the uncertainty surrounding some of these outcomes, especially those related to sexual function, in which the data are sparse and usually available for only a subset of participants in each study, as was highlighted by one review (79). Furthermore, many of these reviews included evidence from non-randomized studies and had an overall low quality(80,81). In some cases, the evidence was synthesised by the authors of the primary studies (73). Finally, there is a paucity of reviews focusing on TUMT in the last few years, considering that no trials are available since the previous version of the Cochrane Review(82).

Conclusions

Minimally invasive treatments may result in similar or worse effects concerning urinary symptoms and quality of life, compared to the standard treatment (transurethral resection of the prostate) at short-term follow-up. They may result in a large reduction of major adverse events, especially in the use of prostatic urethral lift and prostatic arterial embolisation, which resulted in better rankings for symptomatic symptoms scores. Prostatic urethral lift may result in fewer retreatments than other interventions, especially transurethral microwave

thermotherapy, which has the highest retreatment rates at long-term follow-up. We are very uncertain about the effects of these interventions on erectile function; however, these treatments may result in fewer cases of ejaculatory dysfunction. Considering that patients value the effects of these treatments on urinary symptoms, retreatment rates, and adverse events, including sexual function, it becomes necessary to engage in shared decision-making when discussing their different treatment options, highlighting the existing uncertainties and eliciting their preferences.

There needs to be better reporting of basic trial methodology and a greater emphasis on patient-reported outcomes, especially those related to sexual function. Many studies broke the blinding period after three months, and patients crossed to the active treatment group, which prevented us from knowing the long-term effects of these interventions. This is particularly relevant for convective radiofrequency water vapour therapy and temporary implantable nitinol device, both of which are supported only by single trials that compared the new therapeutic approach to sham control, with a three-month time horizon. Sham-controlled trials provide only limited and indirect evidence to inform decision-making, and future research could focus on active comparisons and patient-important outcomes with a follow up greater than 12 months (65,66,83). A core outcome set should establish which outcomes should be collected and how and when they should be collected.

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Contributions of authors

JVAF: conception and study design and drafting the protocol, data extraction and analysis, writing the full review. JHJ: drafting the protocol, data extraction and analysis, writing the full review. MI: drafting the protocol, providing clinical input and approving the final draft. MB: drafting the protocol, providing clinical input and approving the final draft. SY: revising the protocol, providing clinical input and approving the final draft. MIO: drafting the protocol, providing clinical input and approving the final draft. JG: providing clinical input and approving the final draft. CMEL: creating search strategies and searching for trials, writing the methods and results section related to the searches and approving the final draft. AAV: drafting the protocol, providing supervision on the statistics and approving the final draft. LG: drafting the protocol, data extraction and analysis, writing the full review. PD: conception and study design, providing clinical and methodological advice on the protocol.

Disclosure of Interests

JVAF, JHJ, MI, JG, MIO, CMEL, AAV, LG, and PD: none known. SY: Boston Scientific (speaker), Galvanize (consultant). MB: Boston Scientific (consultant for endourology and stone management), Auris Health (consultant for robotic surgery and endourology), Urotronic (disease monitoring and safety board).

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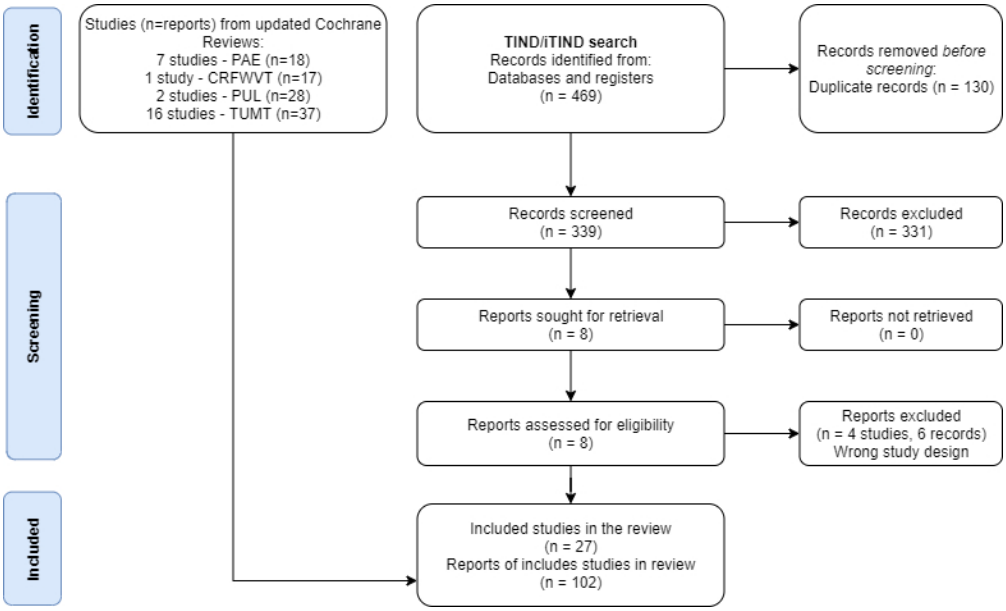

PRISMA flow diagram

275x166mm (72 x 72 DPI)

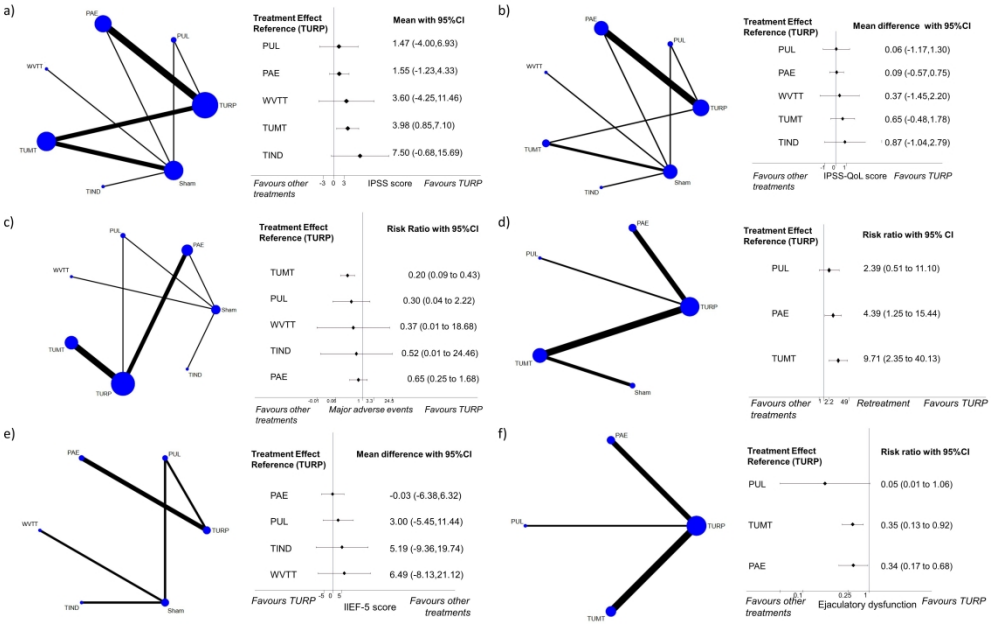

Figure 2. Network maps and forest plots.

1289x831mm (96 x 96 DPI)

Table 1. Characteristics of the included studies

Study name	Trial period	Country	Description of participants	Intervention and comparator	Duration of follow-up	Age*	IPSS*	Prostate volume*
Convective radiofrequency water vapor thermal therapy (WVTT)								
McVary 2016	2013-2014	USA	Men ≥ 50 years; symptomatic BPH with IPSS ≥ 13; Qmax 5-15 mL/s voided volume ≥ 125 mL; prostate volume 30-80 g	WVTT	3 months	63 ± 7.1	22 ± 4.8	45.8 ± 13.0
				Sham		62.9 ± 7.0	21.9 ± 4.7	44.5 ± 13.3
Prostatic arterial embolization (PAE)								
Abt 2018	2014-2017	Switzerland	Men ≥ 40 years, refractory symptoms, prostate 25-80 mL, with IPSS ≥ 8, IPSS-QoL ≥ 3, with Qmax < 12 mL/s or urinary retention	PAE	24 months	65.7 ± 9.3	19.38 ± 6.37	52.8 ± 32.0
				TURP		66.1 ± 9.8	17.59 ± 6.17	56.5 ± 31.1
Carnevale 2016	2010-2012	Brazil	Men > 45 years; IPSS > 19; refractory symptoms > 6 months; prostate 30-90 mL; bladder outlet obstruction (urodynamic examination)	PAE	12 months	63.5 ± 8.7	25.3 ± 3.6	63.0 ± 17.8
				TURP		66.4 ± 5.6	27.6 ± 3.2	56.6 ± 21.5
Gao 2014	2007-2012	China	Men with IPSS > 7 after failed medical therapy, prostate volume 20-100 mL, Qmax < 15 mL/sec	PAE	24 months	67.7 ± 8.7	22.8 ± 5.9	64.7 ± 19.7
				TURP		66.4 ± 7.8	23.1 ± 5.8	63.5 ± 18.6
Insausti 2020	2014-2017	Spain	Men > 60 years; LUTS refractory to medical treatment >6 months; IPSS ≥ 8; IPSS-QoL ≥ 3; Qmax ≤ 10 mL/s or urinary retention	PAE	12 months	72.4 ± 6.2	25.8 ± 4.64	60.0 ± 21.6
				TURP		71.8 ± 5.5	26.0 ± 7.29	62.8 ± 23.8
Pisco 2020	2014-2018	Portugal	Men > 45 years; severe LUTS; IPSS ≥ 20 and IPSS-QoL ≥ 3 > 6 months' treatment with alpha-blockers; Qmax < 12 mL/s; prostate volume 40 mL	PAE	6 months	64	25.5	63.5
				Sham		64	27.5	66
Radwan 2020	2016-2018	Egypt	Men with LUTS with an IPSS score of 8 to 35, Qmax ≤ 10 mL/s; prostate volume < 100 mL	PAE	6 months	63.0 ± 7.2	27.0 ± 5.0	58.7 ± 23.4
				TURP		62.0 ± 9.0	26.5 ± 4.0	60.1 ± 21.5

Zhu 2018	2016	China	Men with a comprehensive diagnosis of BPH through ultrasound prostate examination, digital rectal examination, IPSS, etc.; no absolute contraindication for surgery; no previous history of surgery; not taking 5-alpha reductase inhibitors	PAE	12 months	61.1 ± 4.4	25.63 ± 4.28	81.21 ± 6.34
				TURP		62.4 ± 4.9	26.22 ± 4.35	82.09 ± 6.47
Prostatic urethral lift (PUL)								
Gratzke 2017	2012-2013	Europe	Men ≥ 50 years with IPSS > 12, Qmax ≤ 15 mL/second for 125 mL voided volume, PRV < 350 mL, prostate volume ≤ 60 mL, sexually active, Incontinence Severity Index score ≤ 4	PUL	24 months	63 ± 6.8	22 ± 5.7	38 ± 12
				TURP		65 ± 6.4	23 ± 5.9	41 ± 13
Roehrborn 2013	2011	19 centres/US, Canada, and Australia	Men ≥ 50 years, AUASI ≥ 13, Qmax ≤ 12 mL/second with a 125 mL voided volume and a 30-80 mL prostate volume	PUL	3 months	67 ± 8.6	22.2 ± 5.48	44.5 ± 12.4
				Sham		65 ± 8.0	24.4 ± 5.75	40.9 ± 10.8
Temporary implantable nitinol device (TIND)								
Chughtai 2020	2015-2018	USA/Canada	Men ≥ 50 years; symptomatic BPH. IPSS ≥ 10, Qmax < 12 ml/sec; voided volume > 125 mL; prostate volume 25-75 ml	TIND	3 months	61.5 ± 6.5	22.1 ± 6.8	43.4 ± 15.5
				Sham		60.1 ± 6.3	22.8 ± 6.2	43.8 ± 13.3
Transurethral microwave thermotherapy (TUMT)								
Abbou 1995	N/A	France	Men ≥ 50 years with symptoms > 3 months, prostate 30-80 g, Qmax < 15 mL/s, PVR < 300 mL	TUMT	12 months	65 ± 8	N/A	45 ± 15
				Sham		66 ± 7	N/A	44 ± 11
Ahmed 1997	N/A	UK	Men ≥ 55 years with AUA score >12 > 1-year, prostate 25-100 mL, Qmax < 15 mL/s and a PVR < 300 mL	TUMT	6 months	69.36	18.5	36.6
				TURP		69.45	18.4	46.1
Albala 2002	N/A	USA	Men 50-80 years, AUA index > 13 and a bother score >11, Qmax < 12 mL/sec and PVR > 125 mL; prostate 30-100 mL without a significant intravesical middle lobe	TUMT	12 months	65.2 ± 7.3	22.2 ± 5.0	50.5 ± 18.6
				Sham		64.6 ± 7.1	22.7 ± 5.7	47.1 ± 17.9
Bdesha 1994	N/A	UK	Men with prostatism (WHO score > 14), PVR > 50 mL, Qmax	TUMT	3 months	63.7	19.2	N/A

			< 15 ml/s	Sham		62.6	18.8	N/A
Blute 1996	N/A	USA	Men suffering from urinary symptoms (Madsen Symptom score >8), PVR 10000 mL, Qmax < 10 mL/s, prostate length 30 – 50 mm	TUMT	12 months	66.9 ± 7.8	19.9 ± 7.2	37.4 ± 14.2
				Sham		66.9 ± 7.1	20.8 ± 6.7	36.1 ± 13.4
Brehmer 1999	N/A	Sweden	Men suffering from lower urinary tract symptoms and with an enlarged prostate	TUMT	12 months	70.4	N/A	N/A
				Sham				
D'Ancona 1998	1994-1995	Netherlands	Men ≥ 45 years with Madsen score > 8 months, prostate 2.5-5 cm/30-100 mL, Qmax < 15 mL/s PRV < 350 mL	TUMT	24 months	69.6 ± 8.5	16.7 ± 5.6	45 ± 15
				TURP		69.3 ± 5.9	18.3 ± 6.3	43 ± 12
Dahlstrand 1995	N/A	Sweden	Men ≥ 45 years with Madsen score > 8 months, prostate 3.5-5 cm, Qmax < 15 mL/s PRV > 150 mL	TUMT	24 months	68	N/A	33
				TURP		79	N/A	37
De Wildt 1996	1991-1992	Netherlands/ UK	Men ≥ 45 years with Madsen score > 8 months, Qmax < 15 mL/s PRV > 150 mL	TUMT	12 months	63.3 ± 8.1	N/A	48.6 ± 16.6
				Sham		66.9 ± 6.0	N/A	49.0 ± 20.0
Floratos 2001	1996-1997	Netherlands	Men ≥ 45 years, prostate ≥ 30 cm3, prostatic urethral length ≥ 25 mm, a Madsen symptom score ≥ 8, Qmax ≤ 15 ml/s, PVR ≤ 350 ml	TUMT	36 months	68	21	42
				TURP		66	20	48
Larson 1998	1994-1996	USA	Men ≥ 45 years with AUA score > 9, enlarged prostate (3-5 cm TRUS), Qmax < 12 mL/s without a significantly enlarged middle lobe	TUMT	12 months	66	20.8	38.1
				Sham		65.9	21.3	44.7
Nawrocki 1997	N/A	UK	Men with a Madsen symptom score ≥ 8, Qmax ≤ 15 ml/s, PVR > 150 ml, detrussor pressure > 70 cm H2O	TUMT	6 months	70	19	41.2 ± 14.6
				Sham			17.5	46.7 ± 16.8
Norby 2002	1996-1997	Denmark	Men ≥ 50 years, IPSS ≥ 7, Qmax ≤ 12 ml/s	TUMT	6 months	66 ± 7	20.5 ± 5.7	43
				TURP/TUIP		68 ± 7	21.3 ± 6.6	44
Roehrborn	N/A	United States		TUMT	6 months	66.3 ± 6.5	23.6 ± 5.6	48.1 ± 16.2

1998			Men ≥ 55 years, AUA-SI ≥ 13, Qmax ≤ 12 ml/s, prostate volume 25-100 mL	Sham		66.0 ± 5.8	23.9 ± 5.6	50.5 ± 18.1
Venn 1995	N/A	UK	Men with a Madsen symptom score ≥ 8, PVR < 250 ml	TUMT	6 months	70.5	19.2	40.4
				Sham		68	20.1	40.6
Wagrell 2002	1998-1999	Scandinavia/ USA	Men IPSS ≥ 13, Qmax ≤ 13 ml/s, prostate volume 30-100 mL	TUMT	5 years	67 ± 8	21.0 ± 5.4	48.9 ± 15.8
				TURP		69 ± 8	20.4 ± 5.9	52.7 ± 17.3

(*) mean/median, ± standard deviation when available. AUA-SI/IPSS score: American Urological Association Symptom Index/International Prostate Symptom Score; BPH: benign prostatic hyperplasia; WVTT: convective radiofrequency water vapour therapy; LUTS: lower urinary tract symptoms; PAE: prostatic arterial embolisation; PSA: prostate-specific antigen; PUL: prostatic urethral lift; PVR: postvoid residual; Qmax: maximum flow rate; TIND: temporary implantable nitinol device; TUMT: transurethral microwave thermotherapy; TURP: transurethral resection of the prostate.

Table 2. Summary of findings table

Patient or population: men with moderate to severe lower urinary symptoms due to benign prostatic hyperplasia **Interventions:** minimally invasive treatments **Comparator (reference):** transurethral resection of the prostate **Setting:** hospital procedure – outpatient follow-up				
Outcome: urinary symptoms scores - Measured by: IPSS range 0-35 (lower scores indicate fewer symptoms) - Follow-up: 3 to 12 months (most of the data is at 3 months follow-up)				
19 studies 1847 participants	**Anticipated absolute effect (95% CI) ***		**Certainty of the evidence**	**Ranking (SUCRA) ****
	With TURP	**With a minimally invasive procedure**		
PUL (UroLift) (mixed estimate)	Mean score in the included studies: 6.82 (range 5.1 to 12.6)[a]	1.47 higher (4.00 lower to 6.93 higher)	⊕⊕⊖⊖ Low	2.8 (70.5%)
PAE (mixed estimate)		1.55 higher (1.23 lower to 4.33 higher)	⊕⊕⊖⊖ Low	2.9 (69.2%)
WVTT (Rezūm) (indirect estimate)		3.60 higher (4.25 lower to 11.46 higher)	⊕⊕⊖⊖ Low	3.9 (52.4%)
TUMT (mixed estimate)		3.98 higher (0.85 higher to 7.10 higher)	⊕⊕⊖⊖ Low	4.4 (43.0%)
TIND (indirect estimate)		7.50 higher (0.68 lower to 15.69 higher)	⊕⊕⊖⊖ Low	5.5 (21.5%)
Outcome: Quality of life - Measured by: IPSS QoL range 0-6 (lower scores indicate a fewer impact on the quality of life) - Follow-up: 3 to 12 months				
13 studies 1469 participants	**Anticipated absolute effect (95% CI) ***		**Certainty of the evidence**	**Ranking (SUCRA) ****
	With TURP	**With MIT**		
PUL (UroLift) (mixed estimate)	Mean score in the included studies: 2.09 (range 0.9 to 3.26)[a]	0.06 higher (1.17 lower to 1.30 higher)	⊕⊕⊖⊖ Low	2.8 (70.3%)
PAE (mixed estimate)		0.09 higher (0.57 lower to 0.75 higher)	⊕⊕⊖⊖ Low	2.9 (68.1%)
WVTT (Rezūm) (indirect estimate)		0.37 higher (1.45 lower to 2.20 higher)	⊕⊕⊖⊖ Low	3.6 (56.3%)

TUMT (mixed estimate)		0.65 higher (0.48 lower to 1.78 higher)	⊕⊕⊖⊖ Low	4.5 (42.2%)
TIND (indirect estimate)		0.87 higher (1.04 lower to 2.79 higher)	⊕⊕⊖⊖ Low	5.0 (33.4%)

Outcome: major adverse events - Defined as Clavien-Dindo Grade III, IV, and V, including hospitalisations and procedures to treat complications related to the initial intervention. - Follow-up: 3-36 months

15 studies 1573 participants	**Anticipated absolute effect (95% CI) ***		**Relative effect (95% CI)**	**Certainty of the evidence**	**Ranking (SUCRA) ****
	With TURP	**With MIT**			
TUMT (mixed estimate)	Median rate of major adverse events: 130 per 1000[a]	104 fewer per 1000 (118 fewer to 74 fewer)	RR 0.20 (0.09 to 0.43)	⊕⊕⊕⊖ Moderate	2.7 (72.1%)
PUL (UroLift) (mixed estimate)		90 fewer per 1000 (125 fewer to 159 more)	RR 0.30 (0.04 to 2.22)	⊕⊕⊖⊖ Low	3.6 (56.9%)
WVTT (Rezūm) (indirect estimate)		81 fewer per 1000 (129 fewer to 870 more)	RR 0.37 (0.01 to 18.68)	⊕⊕⊖⊖ Low	4.0 (50.0%)
TIND (indirect estimate)		63 fewer per 1000 (129 fewer to 870 more)	RR 0.52 (0.01 to 24.46)	⊕⊕⊖⊖ Low	4.3 (44.7%)
PAE (mixed estimate)		45 fewer per 1000 (97 to 89 more)	RR 0.65 (0.25 to 1.68)	⊕⊕⊖⊖ Low	5.0 (33.6%)

Outcome: retreatment - Defined as the number of participants requiring a follow-up procedure for lower urinary tract symptoms including another minimally invasive treatment or TURP (this does not include procedures to treat complications - these are included under major adverse events) - Follow-up: 12 - 60 months

10 studies 799 participants	**Anticipated absolute effect (95% CI) ***		**Relative effect (95% CI)**	**Certainty of the evidence**	**Ranking (SUCRA) ****
	With TURP	**With MIT**			
PUL (UroLift) (mixed estimate)	Median rate of retreatment: 12 per 1000[a]	17 more per 1000 (6 fewer to 121 more)	RR 2.39 (0.51 to 11.10)	⊕⊖⊖⊖ Very low	2.2 (68.8%)
PAE (mixed estimate)		41 more per 1000 (3 more to 173 more)	RR 4.39 (1.25 to 15.44)	⊕⊖⊖⊖ Very low	3.0 (50.8%)
TUMT (mixed estimate)		104 more per 1000 (16 more to 470 more)	RR 9.71 (2.35 to 40.13)	⊕⊕⊕⊖ Low	3.7 (32.1%)
WVTT (Rezūm) (pairwise)	We are very uncertain about the effects of WVTT on retreatment compared to sham at three months follow-up (RR 1.36, 95% CI 0.06 to 32.86, 1 study, 197 participants).			⊕⊖⊖⊖ Very low	Not in NMA

TIND (pairwise)	We are very uncertain about the effects of TIND on retreatment compared to sham at three-month follow-up (RR 0.67, 95% CI 0.11 to 3.89, 1 study, 185 participants).	⊕⊖⊖⊖ Very low	Not in NMA

Outcome: erectile function - Measured by: IIEF scores range 5-25 (higher scores indicate better function) - Follow-up 3 to 12 months

6 studies 640 participants	**Anticipated absolute effect (95% CI) ***		**Certainty of the evidence**	**Ranking (SUCRA) ****
	With TURP	**With MIT**		
WVTT (Rezūm) (indirect estimate)	Mean score in the included studies: 15.16 (range 11.67 to 17.70)[a]	6.49 higher (8.13 lower to 21.12 higher)	⊕⊖⊖⊖ Very low	2.5 (70.7%)
TIND (indirect estimate)		5.19 higher (9.36 lower to 19.74 higher)	⊕⊖⊖⊖ Very low	2.9 (61.7%)
PUL (UroLift) (mixed estimate)		3.00 higher (5.45 lower to 11.44 higher)	⊕⊖⊖⊖ Very low	3.5 (49.5%)
PAE (mixed estimate)		0.03 lower (6.38 lower to 6.32 higher)	⊕⊖⊖⊖ Very low	4.4 (31.1%)
TUMT	Not reported			

Outcome: ejaculatory function - Defined as: men with ejaculatory dysfunction - loss or substantial reduction in ejaculation (as an indication of retrograde ejaculation) - Follow-up: 3 to 12 months

8 studies 461 participants	**Anticipated absolute effect (95% CI) ***		**Relative effect (95% CI)**	**Certainty of the evidence**	**Ranking (SUCRA) ****
	With TURP	**With MIT**			
PUL (UroLift) (mixed estimate)	Median rate of ejaculatory dysfunction: 550 per 1000[a]	521 fewer per 1000 (549 fewer to 32 more)	RR 0.05 (0.01 to 1.06)	⊕⊖⊖⊖ Very low	1.2 (92.1%)
TUMT (mixed estimate)		364 fewer per 1000 (458 fewer to 173 fewer)	RR 0.34 (0.17 to 0.68)	⊕⊖⊖⊖ Very low	2.3 (55.1%)
PAE (mixed estimate)		356 fewer per 1000 (476 fewer to 42 fewer)	RR 0.35 (0.13 to 0.92)	⊕⊖⊖⊖ Very low	2.5 (51.1%)
WVTT (Rezūm) (pairwise)	Based on one study with 131 participants, WVTT may result in little to no difference in events of ejaculatory dysfunction compared to sham at short-term follow-up (RR 4.01, 95% CI 0.22 to 72.78).			⊕⊖⊖⊖ Very low	Not in NMA

TIND (pairwise)	The study assessing TIND compared to sham reported no events of ejaculatory dysfunction.	⊕⊖⊖⊖ Very low	Not in NMA

* Estimates are reported as risk difference and confidence interval (CI). ** Rank statistics is defined as the probability that a treatment out of n treatments in a network meta-analysis is the best, the second, the third, and so on until the least effective treatment. Between brackets the surface under the curve (SUCRA) estimates. **MIT**: minimally invasive treatment. **CI**: confidence interval; **WVTT (Rezum)**: convective radiofrequency water vapour thermal therapy; **IPSS**: International Prostate Symptom Score; **NMA**: network meta-analysis; **PAE**: prostatic arterial embolisation; **PUL (Urolift)**: prostatic urethral lift; **RR**: risk ratio; **SUCRA**: surface under the cumulative ranking curve; **TIND**: temporary implantable nitinol device; **TUMT**: transurethral microwave thermotherapy; **TURP**: transurethral resection of the prostate. GRADE Working Group grades of evidence (or certainty of the evidence): **High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect. **Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. **Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the effect estimate. **Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.