Clinical review

Extracts from "Clinical Evidence"

Benign prostatic hyperplasia

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Interventions

Beneficial:

α Blockers

5α Reductase inhibitors

Transurethral resection (TURP)

Transurethral microwave thermotherapy (TUMT)

Transurethral needle ablation (TUNA)

Likely to be beneficial:

Saw palmetto plant extracts

β Sitosterol plant extracts

Rye grass pollen extract

Unknown effectiveness:

TURP versus less invasive surgical techniques

Background

Definition Benign prostatic hyperplasia (BPH) is defined histologically. Clinically, it is characterised by lower urinary tract symptoms (urinary frequency, urgency, a weak and intermittent stream, needing to strain, a sense of incomplete emptying, and nocturia), and can lead to complications, including acute urinary retention.

Incidence/prevalence Estimates of the prevalence of symptomatic BPH range from 10-30% for men in their early 70s, depending on how BPH is defined.[1]

Aetiology/risk factors The mechanisms by which BPH causes symptoms and complications are unclear, although obstruction of the bladder outlet is an important factor.[2] The best documented risk factors are increasing age and functioning testes.[3]

Prognosis Community and practice based studies suggest that men with lower urinary tract symptoms can expect slow progression of the symptoms.[4,5] However, symptoms can wax and wane without treatment. In men with symptoms of BPH, rates of acute urinary retention range from 1-2% a year.[5–7]

Aims To reduce or alleviate lower urinary tract symptoms; to prevent complications; and to minimise adverse effects of treatment.

Outcomes Burden of lower urinary tract symptoms; rates of acute urinary retention and prostatectomy; rates of adverse effects of treatment. Symptoms are measured using the validated international prostate symptom score, which includes seven questions quantifying symptoms on an overall scale from 0-35, with higher scores representing more frequent symptoms

Methods

Clinical Evidence update search and appraisal August 2000. This review is currently being updated and will be available on the *Clinical Evidence* website in December 2001.

Question What are the effects of medical treatments?

Option α Blockers

Summary Two systematic reviews have found that α blockers are more effective than placebo for improving lower urinary tract symptoms in men with BPH. Two randomised controlled trials (RCTs) found limited evidence that α blockers were more effective in improving symptoms than 5α reductase inhibitors. We found no direct comparison of α blockers with surgical treatment.

Benefits

Versus placebo: We found two systematic reviews (search date 1998, 21 RCTs,[9] and 1999, 24 RCTs[10]). Most RCTs found a greater improvement in symptoms with α blockers than with placebo (results presented graphically or in tabular form; overall significance not stated). The largest RCT (2084 men with BPH) compared terazosin at doses of up to 10 mg daily for one year against placebo. Treatment achieved significantly greater mean improvement in international prostate symptom score (−7.6 points from baseline with terazosin *v* −3.7 with placebo; mean change, terazosin *v* placebo −3.9 points, 95% confidence interval −5.5 points to −3.3 points).[11] We found insufficient evidence on the effect of α blockers on complications of BPH. One small RCT found sustained release alfuzosin (5 mg twice daily) for 48 hours increased the ability to pass urine after catheter removal in men catheterised for acute retention, from 5% to 29% (number needed to treat (NNT) 4).[12] **Versus each other:** The first systematic review[9] identified three head to head comparisons that reported

clinical outcomes, and we found three subsequent RCTs of limited quality.[13–15] The largest RCT in the review (256 men) compared tamsulosin against alfuzosin.[12] The second RCT (103 men) compared alfuzosin against prazosin, and the third trial (98 men) compared tamsulosin against terazosin. The RCTs found no significant difference in symptom score among α blockers. The first subsequent RCT (212 men) found that tamsulosin improved total international prostate symptom score compared with terazosin (9.7% change from baseline with tamsulosin *v* 8.5% with terazosin; $P<0.05$).[13] The second subsequent RCT (61 men) compared terazosin against tamsulosin and found no significant difference in international prostate symptom score.[14] The third RCT comparing terazosin against alfuzosin also found no significant difference in the score.[15] **Versus 5α reductase inhibitors:** We found no systematic review. We found two RCTs of limited quality (see comment below). One RCT (1229 men with a diagnosis of BPH) compared finasteride against an α blocker or against both treatments combined.[16] Terazosin was associated with a greater reduction in symptoms than finasteride, regardless of prostate size. The difference in mean international prostate symptom scores at one year was 2.9 points. There was no significant difference between treatment with both agents compared with terazosin alone. The second RCT (1051 men) compared alfuzosin against finasteride against both drugs combined over six months. It found that alfuzosin compared with finasteride significantly decreased the mean international prostate symptom score from baseline, and found no significant difference between alfuzosin alone compared with combination therapy.[17] **Versus transurethral microwave thermotherapy (TUMT):** See TUMT.

Harms

The first systematic review found that withdrawals attributed to adverse events were similar for alfuzosin, tamsulosin (0.4 mg dose), and placebo (results were presented graphically; significance not stated).[9] However, a higher withdrawal rate was found with doxazosin, terazosin, and tamsulosin (0.8 mg dose). There was little observable difference between the number of men experiencing dizziness with alfuzosin or tamsulosin compared with placebo (results were presented graphically; significance not stated). However, more men experienced dizziness after terazosin and doxazosin than placebo (results were presented graphically; significance not stated). One large RCT included in the systematic review compared tamsulosin against a less selective α blocker, alfuzosin. It found that adverse effects were similar: dizziness occurred in 7%, asthenia in 2%, and postural hypotension in 2%.[9] One RCT from China compared low dose terazosin (2 mg daily) and tamsulosin (0.2 mg daily). It found dizziness (32% *v* 10%) and hypotension limiting therapy (9% *v* 1%) were more common with terazosin.[13] Both selective and less selective α blockers may be associated with abnormal ejaculation: the risk of abnormal ejaculation was higher with tamsulosin than placebo (4.5% *v* 1%) but similar with tamsulosin and alfuzosin (0.8% *v* 0%).[18] **Versus 5α reductase inhibitors:** In the trial comparing terazosin against finasteride, dizziness was seen in about 25% of men taking terazosin, generalised weakness in 15%, rhinitis in 8%, and postural hypotension in 8%, whereas sexual dysfunction was more common in men taking finasteride.[16]

Comment

Men with severe symptoms can expect the largest absolute fall in their symptom scores with medical treatment.[11 19] Prazosin, alfuzosin, terazosin, and doxazosin lower blood pressure and may be used to treat both hypertension and BPH.[20] The three subsequent RCTs comparing α blockers are limited by their small sample sizes, short duration (4,[13]4[14] and 16[15] weeks), low drug doses, and unclear methods of randomisation and blinding.

Option 5α Reductase inhibitors

Summary One systematic review has found that 5α reductase inhibitors are more effective than placebo for improving lower urinary tract symptoms and reducing complications in men with BPH, especially in men with larger prostates (≥40 g). Two RCTs found limited evidence that 5α reductase inhibitors were less effective at improving symptoms than α blockers. We found no direct comparison with surgical treatment.

Benefits

Versus placebo: We found one systematic review (search date 1999, 12 RCTs),[10] two non-systematic reviews,[21 22] and one subsequent RCT (published numerous times).[7 23–26] The systematic review found that finasteride compared with placebo significantly reduced symptom scores (10 RCTs, results presented in tabular form; overall significance not stated).[10] The first non-systematic review (meta-analysis, published in 1996) combined the results of six RCTs of finasteride.[21] Treatment compared with placebo was associated with a significantly greater reduction in symptom scores (difference in symptom score −0.9 points, −1.2 to −0.6; range of score 0-30 points). The benefit over placebo was greatest in men with larger prostates (>40 g). The second non-systematic review (meta-analysis, published in 1997) combined the results of three placebo controlled RCTs of finasteride.[22] Finasteride reduced the two year risk of acute urinary retention requiring catheterisation from 2.7% to 1.1% (NNT 62), of progression to prostatectomy from 6.5% to 4.2% (NNT 44), and of either event from 7.5% to 4.9% (NNT 38). The subsequent RCT (3040 men with enlarged prostates and symptoms of BPH) compared finasteride 5 mg daily against placebo.[7] After four years of treatment, finasteride compared with placebo significantly reduced symptoms (difference in symptom score −1.6 points, −2.5 to −0.7; range of score 0-34 points). Finasteride reduced the risk of acute urinary retention significantly more than placebo (6.6% *v* 2.8%; NNT 26, 22 to 38), of prostatectomy (8.3% *v* 4.2%; NNT 24, 19 to 37), and of the risk of either event (13.2% *v* 6.6%; NNT 15, 12 to 20). There was a greater effect among men with higher concentrations of prostate specific antigen at baseline (3.3-12.0 ng/ml), reflecting larger prostates (risk of either acute urinary retention or of needing prostatectomy was 19.9% with placebo *v* 8.3% with finasteride; NNT 8, 7 to 11).[24] This RCT also found that, after four years, finasteride produced a larger fall in international prostate symptom score than did placebo. The fall was greater for men with prostate specific antigen concentrations >1.3 ng/ml than with men with concentrations ≤1.3 ng/ml.[23] **Versus α blockers:** See α blockers. We found two RCTs. Neither trial selected men on the basis of prostate size.[16 17]

Harms

The most common adverse events associated with finasteride in the first year were decreased libido (6%), impotence (8%), and decreased ejaculation (4%). After the first year of treatment, there was no significant difference in adverse effects between finasteride and placebo.[7] Although finasteride reduced concentrations of prostate specific antigen by an average of 50% (individual responses were highly variable), its use for up to four years did not change the rate of detection of prostate cancer compared with placebo.[7] **Versus α blockers:** See α blockers.

Comment

The meta-analysis of finasteride's impact on symptoms at one to two years found that finasteride was significantly more effective than placebo in men with larger prostates.[21] However, the absolute difference in mean decrease of symptom score from baseline between men with the smallest and

largest prostates was only about one point. The relative effectiveness of finasteride compared with placebo also seemed higher in men with slightly raised concentrations of prostate specific antigen,[23] and it is assumed that the higher concentration is a proxy for a larger prostate.

Question What are the effects of surgical treatments?

Option Transurethral resection (TURP)

Summary We found limited evidence from two RCTs that TURP is more effective than watchful waiting for improving symptoms and reducing complications and that it does not increase the risk of erectile dysfunction or incontinence. We found no good long term comparisons of TURP with medical treatments or with newer, less invasive techniques such as transurethral incision, laser ablation, and electrovaporisation.

Benefits

We found no recently updated systematic reviews. **Versus watchful waiting:** We found two RCTs comparing TURP against conservative treatment.[27 28] The first RCT (556 men with moderate symptoms of BPH) compared TURP against watchful waiting.[27] More men receiving TURP improved (90% *v* 39%) and had reduced symptoms than with watchful waiting. After five years, the treatment failure rate was 21% with TURP compared with 10% with watchful waiting (NNT 9, 7 to 17), and 36% of men assigned to watchful waiting had crossed over to surgery.[29] Treatment failure was defined as death, acute urinary retention, high residual urine volume, renal azotaemia, bladder stones, persistent incontinence, or a high symptom score. The major categories of treatment failure reduced by TURP were acute urinary retention, development of a large bladder residual (>350 ml), and deterioration to a severe symptom level. The second RCT (223 men) had a shorter duration of follow up (7.5 months).[28] It found that TURP improved the international prostate symptom score significantly more than conservative treatment (difference 10.4 points, 8.5 to 12.3). **Versus less invasive techniques:** Numerous small RCTs have found similar outcomes for symptoms with TURP and with transurethral incision of the prostate (TUIP) in men with smaller prostates. In the RCT with the longest follow up (120 men, mean follow up 34 months), outcomes were similar for TURP and TUIP.[30] Long term symptom relief and effect on the incidence of complications of BPH have not yet been adequately evaluated. Two recently reported trials comparing older laser techniques against TURP found higher surgical retreatment rates after laser therapy (38% *v* 16% at 5 years with a side firing laser,[31] and 18% *v* 9% at 3 years with a contact laser).[32] Several small short term RCTs (maximum 2 years) found either no significant difference between TURP and laser ablation or electrovaporisation,[28 33–42] or that TURP achieved better symptom relief. **Versus TUMT and transurethral needle ablation (TUNA):** See TUMT below, and TUNA.

Harms

Analysis of administrative data found that mortality in the 30 days after TURP for BPH ranged from 0.4% for men aged 65-69 to 1.9% for men aged 80-84 and has fallen in recent years.[43] In one review of observational studies, TURP for BPH was associated with immediate surgical complications in 12% of men, bleeding requiring intervention in 2%, erectile dysfunction in 14%, retrograde ejaculation in 74%, and incontinence in about 5%.[44–46] Analysis of claims data found a reoperation rate, implying need for retreatment, of about 1% a year.[43] However, in the only comparative trial, men randomised to prostatectomy did not seem to have a greater rate of erectile dysfunction or incontinence than men assigned to watchful waiting.[27 29] Laser prostatectomy and electrovaporisation require less hospital time and may cause fewer short term adverse effects and less bleeding than TURP.[28 33–38 42 47 48]

Comment

Rapid changes in techniques and few controlled trials with adequate follow up make comparisons between TURP and newer surgical techniques difficult.

Option Transurethral microwave thermotherapy (TUMT)

Summary RCTs have found that TUMT in comparison to sham treatment significantly reduces symptoms of BPH. We found conflicting evidence about whether TUMT relieves short term symptoms as effectively as TURP. One RCT found limited evidence that TUMT was more effective than α blockers over six months.

Benefits

We found no systematic review. **Versus sham treatment:** Several small to medium sized RCTs compared TUMT against sham treatment. In the largest trial (220 men), TUMT improved the international prostate symptom score significantly more than sham treatment (5.0 points lower, $P<0.05$).[49] **Versus TURP:** Two small trials with follow up to 2.5 years found no difference in symptom relief between TUMT and TURP.[50 51] A third trial found better symptomatic outcomes with TURP (significance not stated).[52] **Versus α blockers:** One RCT (103 men) compared TUMT against terazosin (up to 10 mg daily) and found significantly better improvement in international prostate symptom score after TUMT at six months.[53]

Harms

Adverse events associated with TUMT varied among trials, but included the need for catheterisation for more than a week (8% with TUMT *v* 2% with sham treatment),[54] persistent irritative symptoms (22% *v* 8%),[49] haematuria (14% *v* 1%),[49] and sexual dysfunction (mostly haematospermia and other ejaculatory abnormalities, 29% *v* 1%).[49] In one trial, retrograde ejaculation was substantially less common after TUMT than TURP (27% *v* 74%).[52]

Comment

TUMT can be performed in an outpatient setting, and uses heat generated by a microwave antennae in the urethra to coagulate prostate tissue. The long term effects of TUMT have not been adequately evaluated in controlled studies.

Option Transurethral needle ablation (TUNA)

Summary We found limited evidence from one RCT that TURP in comparison to TUNA reduced symptoms of BPH, although TUNA caused fewer adverse effects.

Benefits

We found no systematic review. **Versus TURP:** We found one RCT (121 men) comparing TUNA against TURP.[55] The mean international prostate symptom score fell from 24.7 to 11.1 points at one year with TUNA, 2.4 points less than the decrease after TURP. Benefit at one year was significantly greater with TURP than TUNA (international prostate symptom score 11.1 with TUNA *v* 8.3 with TURP, $P=0.04$).

Harms
Compared with TURP, TUNA was associated with less retrograde ejaculation (38% *v* 0%) and bleeding (100% *v* 32%).[55]

Comment
TUNA can be performed in an outpatient setting, and uses radiofrequency energy through two intraprostatic electrodes to generate heat to coagulate prostate tissue. Anaesthesia requirements vary in reported studies. The long term effects of treatment have not been adequately evaluated.

Question What are the effects of non-medical treatments?

Option Saw palmetto plant extracts

Summary One systematic review has found that self rated improvement is better in men taking saw palmetto than in those taking placebo. It found no significant difference in symptom scores between saw palmetto and finasteride.

Benefits
We found one systematic and one non-systematic review. The systematic review (search date 1997, 18 RCTs, 2939 men) included all saw palmetto preparations[56]; the non-systematic review (11 RCTs) included only one pure saw palmetto preparation.[57] **Versus placebo:** The systematic review found that patient rated improvement was better in men taking saw palmetto than placebo (6 RCTs, RR 1.7, 1.2 to 2.4). It found a significant difference in nocturia in men receiving saw palmetto compared with placebo (10 RCTs, weighted mean difference (WMD) of 0.76 episodes per night, 0.32 to 1.21). The non-systematic review focused only on nocturia and found similar results.[57] **Versus finasteride:** The systematic review found similar symptom scores with saw palmetto and finasteride.[56]

Harms
In the systematic review, withdrawal rates were significantly higher with saw palmetto than placebo (9% *v* 7%, P = 0.02), and not significantly different from finasteride (9% *v* 11%, P = 0.87). The risk of erectile dysfunction was similar with saw palmetto and placebo (1.1% *v* 0.7%, P = 0.58), but was significantly lower in comparison to finasteride (1.1% *v* 4.9%, P < 0.001).[56]

Comment
The RCTs were brief and few used a validated symptom score. Different preparations, which may not be equivalent, are available directly to consumers without prescription in many countries.

Option β Sitosterol plant extract

Summary One systematic review found that β sitosterol plant extract compared with placebo significantly improved lower urinary tract symptoms in the short term.

Benefits
Versus placebo: We found one systematic review (search date 1998, 4 RCTs, 519 men), which compared β sitosterol and placebo.[58] Trials lasted 4-26 weeks. It found that β sitosterol significantly reduced the international prostate symptom score (2 RCTs, WMD −4.9 points, −6.3 to −3.5).

Harms
Gastrointestinal adverse effects occurred in more men taking β sitosterol than placebo (1.6% *v* 0%, significance not stated). Impotence was also more common in men taking β sitosterol (0.5% *v* 0%, significance not stated). Withdrawal rates were similar in both groups (7.8% in men taking β sitosterol *v* 8.0% taking placebo, significance not stated).[58]

Comment
The RCTs were limited by a short follow up period (maximum 26 weeks). Different preparations are available, which may be of variable content, making it difficult to generalise results.

Option Rye grass pollen extract

Summary One systematic review found limited evidence that rye grass pollen extract compared with placebo increased self rated improvement and reduced nocturia in the short term.

Benefits
Versus placebo: We found one systematic review (search date 1998, 2 RCTs, 163 men), which compared rye grass pollen extract against placebo.[59] Pollen extract significantly increased self rated improvement (1 RCT, 60 men; 69% *v* 29%; RR 2.40, 1.21 to 4.75), and significantly reduced nocturia (2 RCTs; absolute risk 50/79 (63%) *v* 23/74 (31%); RR 2.05, 1.41 to 3.99). However, the results should be interpreted with caution; see comment below.

Harms
The review found that nausea occurred in one man taking pollen extract (number in placebo group not stated). Withdrawal rates were not significantly different (4.8% with pollen extract *v* 2.7% with placebo, P = 0.26).[59]

Comment
Both RCTs were limited by small sample sizes and a short follow up period (12 and 24 weeks). Concealment of treatment allocation was unclear. The composition of the preparations was unknown, making it difficult to generalise results.

This topic is currently being updated. The update will be available on the *Clinical Evidence* website by the end of the year.

Competing interests: CR has received a fee for consulting, speaking, research, and/or running educational programs for Merck, Sharpe & Dohme, GlaxoWellcome, Sanofi-Synthelabo, and Urologix.

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Endpiece

Foolish idea

To patent the polio vaccine would be "like patenting the sun."

Jonas Salk