The clinical effectiveness of transurethral incision of the prostate – a systematic review of randomised controlled trials

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ABSTRACT

**Purpose:** Transurethral incision of the prostate gland (TUIP) is perceived as a less morbid surgical alternative to standard transurethral resection of the prostate gland (TURP) for treatment of symptomatic mild to moderate benign prostate enlargement (BPE). We aimed to evaluate comparative clinical effectiveness of the two procedures.

**Methods:** Systematic review and meta-analysis of short and long-term data from randomised controlled trials comparing TUIP with TURP.

**Results:** This review considered data from 795 randomised participants across 10 RCTs of moderate to poor quality eight of which stated an upper limit for prostate size. No difference in the degree of symptomatic improvement was seen between the two procedures. Improvement in peak urine flow rate was lower for TUIP compared to TURP whilst the rate of blood transfusion and TUR syndrome was higher after TURP. Urinary retention, urinary tract infection, strictures and incontinence did not differ between the two approaches, although clinically important differences could not be ruled out. TUIP was associated with a shorter duration of operation and length of hospital stay but a higher re-operation rate.

**Conclusion:** TUIP and TURP appear to offer equivalent symptomatic improvement for men with mild to moderate BPE. Choosing TUIP involves a trade-off between the lower risk of peri-operative morbidity and the higher risk of subsequent re-operation.
INTRODUCTION

Lower urinary tract symptoms (LUTS) presumed due to clinical benign prostate enlargement (BPE) are common, affecting up to 40% of men over 70 years of age [1]. Long-term studies show the progressive nature of clinical BPE related to hyperplasia of the stromal and urothelial components of the gland with both International Prostate Symptom Score (IPSS) and prostate volume increasing with age [2].

The aim of treating BPE is to improve bothersome LUTS and associated quality of life, and to prevent or lessen complications such as urinary retention, infection and deteriorating renal function. Treatment options range from self-monitoring of mild symptoms to drugs and on to surgical intervention.

Surgical treatment of clinical BPE has evolved since the work of Guthrie in the 19th century [3] with the development of various endoscopic techniques each with specific advantages and disadvantages; two such techniques are transurethral resection of prostate (TURP) involving diathermy resection of the inner component of the prostate gland, and transurethral incision of prostate (TUIP) involving longitudinal incision of the prostate gland, allowing widening of the bladder neck and prostatic urethra without removal of prostate tissue. Adverse effects associated with TURP such as bleeding, cardiovascular imbalance and sexual dysfunction have driven the search for less invasive alternatives [4]. TUIP has been trialled as a less morbid alternative for men with prostate glands < 30 ml in size, with the suggested advantage of less bleeding and sexual dysfunction [5]. As part of a wide ranging review of surgical treatments for BPE commissioned by the United Kingdom National Institute for Health Research [6], we aimed to evaluate the comparative clinical effectiveness of TUIP against TURP by means of a systematic review of available randomised controlled trials (RCTs).
METHODS

Searching for the evidence

Highly sensitive electronic searches, using a combination of database-specific subject headings and text terms, were developed to identify published and unpublished reports of relevant RCTs evaluating the effectiveness of TUIP and TURP for BPE. Bibliographic databases searched including Medline, Embase, Biosis, Science Citation Index, The Cochrane Library, and trials registers. All searches were carried out during March 2006. Recent conference proceedings (European Association of Urology, American Urological Association and the British Association of Urological Surgeons) for the years 2002-5 were also screened. Searches were not restricted by publication year or language. Reference lists of all included studies were scanned to identify additional potentially relevant studies. Full details of the search strategies used have been published [6] or are available from the authors. The titles and abstracts of all papers identified by the search strategy were screened and full-text copies of all potentially relevant studies obtained.

Selection and study characteristics

Individual RCTs of TUIP compared to TURP for BPE were included. Trials reporting men without a clinical diagnosis of BPE were excluded as well as comparisons against conservative management. The pre-specified outcomes are listed in Table 1. Symptom scores measured by the IPSS, the American Urological Association Symptom Index (AUA), or Madsen-Iversen score were eligible. IPSS and AUA scores were considered equivalent and therefore trials using these instruments were combined. The IPSS/AUA symptom questionnaire asks men to rate four voiding symptoms (poor stream, intermittent flow, straining, incomplete emptying) and three storage symptoms (frequency, nocturia, urgency) on a scale from 0 (not present) to 5 (severe) to give a total score ranging from 0 to 35, with symptom severity defined as: mild (0-7), moderate (8-19) or severe (20-35). With Madsen-Iversen scores, patients are rated in terms of the quality of their urinary stream, straining to void, hesitancy, intermittency, bladder emptying, stress incontinence or post void dribbling, urgency, frequency, and nocturia on a scale from 0 to 4 to give a total score ranging from 0 to 27, with symptom severity defined as: mild (<10), moderate (10-20) or severe (>20). All reports of pre-specified complications were considered regardless of their timing. Bladder neck stenosis and urethral stricture were combined since separate reporting of these complications was inconsistent.
Quality assessment strategy
Two reviewers, working independently, assessed the methodological quality of included studies using an assessment tool drawing on the schema suggested by the NHS Centre for Reviews and Dissemination [7-9].

Data extraction strategy
The titles and abstracts of all papers identified by the search strategy were screened. Two reviewers independently assessed full-text copies of all potentially relevant studies and extracted data from the included studies. The two reviewers recorded details of methodology, interventions, participants’ characteristics and outcomes on a data extraction form. Those differences that could not be resolved through discussion were decided by an arbiter. Reviewers were not blinded to the names of the studies’ authors, institutions or sources of the reports.

Data synthesis
For trials with multiple publications, only the most complete report for each outcome was included (Appendix). Meta-analysis was performed by combining dichotomous outcome data using the Mantel-Haenszel relative risk (RR) method and for continuous outcome data using the inverse variance weighted mean difference (WMD) method and 95% confidence intervals. Fixed effects models were used for all analyses except peak flow and symptom score where random effects were used due to variability in reporting and statistical heterogeneity (assessed using I- and Chi-squared tests). Other possible reasons for heterogeneity were explored using sensitivity analyses. The meta-analyses were conducted using the standard Cochrane software RevMan 4.2.8.

Due to the lack of uniformity of the data presented by many studies, a qualitative review looking for consistency between studies was also performed. This was supplemented, where appropriate by considering the consistency in the direction of effects using the sign-test.
**RESULTS**

We assessed full-text copies of 621 published articles concerning TURP and TUIP to yield 10 RCTs meeting inclusion criteria for the review which were published in 14 reports and described outcome in 795 men recruited between 1985 and 1991, 392 of whom underwent TUIP and 403 TURP [10-22]. An upper limit of prostate size was explicitly stated as an entry criterion for eight studies with five < 30 ml and three < 60 ml.

**Quality and characteristics of available evidence**

All RCTs were of similar poor to moderate quality, with the majority failing to provide details about randomisation, treatment allocation concealment and whether the analyses included an intention to treat analysis (Table 2). The included data allowed comparison of 10 relevant outcomes involving 795 participants. Included studies varied in relation to settings and baseline characteristics of the patients, such as severity of the disease and prostate size (Table 3).

**Assessment of effectiveness**

**Symptom scores**

Five [11,13,15,16] studies provided information on symptom scores for patients at 12 months after treatment. Four of these reported change in Madsen-Iversen scores, one reported IPSS scores [18]. Losses to follow-up were high in nearly all studies reporting 12 months follow-up. No clear pattern emerged (sign test, p < 0.375): three favoured TURP, one TUIP, and one showed no difference. Only two studies presented data in a form suitable to allow meta-analysis, which showed that the direction of effect was not consistent across the studies (IPSS: mean difference (MD) -1.00, 95% CI -1.73 to -0.27, p = 0.007; Madsen-Iversen: MD 0.34, 95% CI -1.55 to 2.23).

**Peak Urine Flow rate**

All five studies [11,13,14,16,17] that provided information on the mean or median peak urine flow rate for patients 12 months after surgery reported lower (worse) mean or median peak urine flow rate following TUIP (sign test p < 0.03). Synthesis of suitable data [16] showed that peak urine flow rate was lower but this did not reach statistical significance (MD -2.71, 95% CI -5.77 to 0.35, p = 0.08).
**Morbidity**

Seven RCTs [11-14,17,19,20] provided information on need for blood transfusion. There were fewer blood transfusions following TUIP in all except one trial [12] reporting no transfusions in either group (Figure 1: 3/266 (11%) versus 77/272 (28%) RR = 0.06, 95% CI 0.03 to 0.16, p < 0.001).

TUR syndrome information was reported in two studies [17,19]. No cases of a TUR syndrome were recorded in patients undergoing TUIP. Conversely, 6.4% of the patients (all in one trial) allocated to TURP had TUR syndrome [17] (Figure 1: 0/139 versus 7/140, RR = 0.07, 95% CI 0.00 to 1.15, p = 0.06).

Meta-analysis of studies reporting data on urinary retention [13,14,15,19], urinary tract infection [17], stricture [11,12,14,15,17,19], and incontinence [14,17,19] showed that there were no statistically significant differences between TUIP and TURP (Figure 1). Clinically important differences could not be ruled-out as the size and direction of effect varied across studies and the confidence intervals were wide. Also, definitions of strictures, incontinence and length of follow-up varied across studies.

Seven studies [11,12,15-17,21] reported sexual dysfunction information. The risk of retrograde ejaculation was lower for men following TUIP than after TURP (Figure 2: 46/195 (23.5%) versus 88/189 (46.5%) RR 0.51, 95% CI 0.38 to 0.68, p < 0.001), whereas, there was no statistically significant difference in terms of erectile dysfunction between the two groups (Figure 2: 4/119 (3.4%) versus 6/103 (5.8%), RR 0.61, 95% CI 0.17 to 2.20, p = 0.45).

**Descriptors of care**

Seven studies [11-15,17,19] provided information on duration of operation and another seven studies [11,12,14,15,17,19,20] detailed length of hospital stay. In all studies duration of operation was shorter in the TUIP group (sign test p < 0.01). Two studies [12, 19] reported data suitable for synthesis and the average duration of TUIP was 18.9 minutes shorter than TURP (Figure 3: 95% CI -24.13 to -13.67, p < 0.001). Meta-analysis of two studies [12, 19] showed that the average length of hospital stay was also significantly shorter following TUIP (Figure 3: WMD -2.26, 95% CI -3.81 to -0.71, p = 0.004). Meta-analysis of six trials showed that the need for re-operation was more common after TUIP than after
TURP [10,11,13-16] (Figure 3: 36/196 (18.4% versus 14/195 (7.2%), RR 2.40, 95% CI 1.37 to 4.21, p < 0.01). It should be noted that differences between studies in timing and completeness of follow-up may have introduced bias and we have therefore tabulated data used for this analysis (Table 4).

**DISCUSSION**

Our search strategy identified 621 articles concerning TURP and TUIP of which 14 reported data from 10 RCTs. The included subjects had mainly mild to moderate BPE. No clear evidence of superiority emerged on meta-analysis regarding our primary outcome of improvement in symptom score at 12 months but analysis was hampered by high drop-out rates and by only two trials reporting data in suitable format. Consideration of a further four trials was supportive of this finding with no consistent pattern of relative effectiveness. A single report found that equivalence of symptomatic benefit persisted for up to five years [13]. In contrast, TURP was clearly superior in terms of urodynamic improvement with a consistent and statistically significant greater increase in peak urinary flow rate [10-17]. The equivalence of patient-reported outcome suggests that men with mild to moderate of BPE would be content with the symptom improvement gained with TUIP. Clinicians however are likely to have some concerns regarding the inferior efficacy of the procedure in correcting bladder outlet obstruction.

To balance this concern, TUIP does demonstrate further advantages in terms of reduced co-morbidity and hospitalisation. Blood transfusion rates are used as a proxy measure of blood loss and were significantly lower with TUIP. It should be noted that subjects recruited for the included trials were all treated prior to 1991. Equipment, peri-operative care and standards of training for urologists performing TURP have all improved over the past 20 years reflected in current transfusion rates of < 2.5% [23]. Avoidance of TUR syndrome appears to be an advantage of TUIP since although a rare complication, it can be life-threatening [17,19]; it should be noted however that prostate size was not explicitly reported by these studies. TUIP did not show advantage in terms of reducing the risk of longer term adverse effects such as urinary incontinence, erectile dysfunction or stricture formation although reporting of these events was inconsistent and important differences could have been missed. Meta-analysis did however confirm lower rates of ejaculatory dysfunction following TUIP with a 50% risk reduction. This is likely to be an important issue for sexually active men with isolated bladder neck
hypertrophy, but this adverse effect does not seem to be bothersome for most men undergoing surgery for BPE [24].

In terms of treatment cost, TUIP shows benefit in terms of reducing operating time and hospital stay but this must be balanced by increased expenditure due to the higher rate of re-operation in the longer term. Ideally these variables would need inclusion with effectiveness data in a formal analysis of cost-effectiveness to determine any overall advantage for TUIP.

In broad terms, results from our systematic review and meta-analysis are in agreement with those published in a previous study by Yang and colleagues [25]. Our review identified two additional studies [18,20] and we were unable to include unpublished data that Yang and colleagues obtained from trial report Authors, but these differences in included data did not affect key findings such as equivalence of symptomatic improvement and superior urodynamic outcome for TURP. In contrast to Yang et al. [25], we found a significantly higher risk of re-operation following TUIP which, if truly reflective of outcome, would have an important bearing on cost-effectiveness. Our decision to exclude data from two trials [12,19] on pre-stated methodological criteria together with differences in statistical methodology used for data synthesis may have contributed to this differing finding, and illustrate that assumptions made during systematic review can change conclusions. Increased re-operation rate following TUIP is a factor that men deciding between the two techniques will have to trade off against decreased risk of adverse effects. For these reasons we feel that the present systematic review does provide a value to the urological community by reinforcing the key findings of Yang and colleagues using a different methodology and by clarifying potentially important differences such as re-operation rates. This will be helpful for those charged with guideline development and makers of health policy.

We used current recommended methodology for this review which included quality assessment of included trials. As has been previously noted [25] trial quality in this area is variable although we do acknowledge the procedural difficulties in conducting and reporting comparative trials of surgical treatments. The majority of studies were conducted and reported prior to the formulation of CONSORT guidelines which may partly explain the wide variation in reporting practice and in particular the fact that results concerning primary outcomes were generally reported in a format
unsuited to meta-analysis. A common failing with such trials is loss to follow-up which compromises the certainty of comparative analysis of long-term outcome, a key measure in the study of treatment of chronic and recurring health problems such as BPE.

Conclusion

This systematic review of available RCTs comparing TUIP and TURP for treatment of mild-moderate BPE has shown TUIP to give equivalent symptomatic improvement accompanied by a reduction in risk of adverse effects. Approximately 2,500 such procedures are carried out annually in England compared to about 25,000 TURP suggesting that it continues to be under-utilised [26]. Ideally an adequately powered, multi-centre RCT comparing TUIP and TURP should be performed but this is unlikely to be funded due to the advancement of other technologies such as laser energy to more safely ablate the prostate together with the long follow-up required to assess reoperation rate. It is possible however that the procedure could be included in long-term ‘tracker’ trials linked to patient or clinician preference to better determine longer term clinical effectiveness and cost-effectiveness.
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CONFLICT OF INTEREST STATEMENT

None.
REFERENCES


