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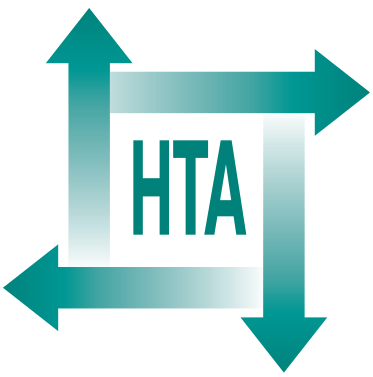

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Randomised evaluation of alternative electrosurgical modalities to treat bladder outflow obstruction in men with benign prostatic hyperplasia

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Abstract

Randomised evaluation of alternative electrosurgical modalities to treat bladder outflow obstruction in men with benign prostatic hyperplasia

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Objectives: To compare and evaluate the clinical and cost-effectiveness of transurethral vaporisation of the prostate (TUVP), a new electrosurgical modality, with the standard treatment, transurethral resection of the prostate (TURP).

Design: A multicentre randomised controlled trial of pragmatic design with associated economic evaluation using cost minimisation.

Setting: Patients were recruited from four centres in south-east England.

Participants: Men requiring surgery for lower urinary tract symptoms deemed to be due to benign prostatic hypertrophy.

Interventions: TURP was performed and subsequent management conducted according to the usual practice of the clinical team. TUVP was performed with the most promising available equipment using a technique described in the literature. Postoperative management after TUVP was left to the ward team, who were not necessarily informed to which treatment arm the patient had been allocated. For the purpose of the study, patients were assessed clinically, by questionnaire and investigation at baseline, 2 months and 6 months after randomisation. A long-term follow-up postal questionnaire was sent to each patient at 2 years. For the economic evaluation, direct costs from the NHS viewpoint were collected.

Main outcome measures: A reduction of at least 5 from the International Prostate Symptom Score (IPSS) was taken as a satisfactory outcome. The IPSS quality of life (QoL) question provided disease-specific information about QoL. Secondary outcome measures included urinary flow rate, post-void urinary volume, prostate volume and pressure-flow urodynamics. Questionnaires used included SF-36, EuroQol and a sexual function section based on the International Continence Society 'Benign Prostatic Hyperplasia' (ICS-BPH) questionnaire. Measurement of full blood count and urea and electrolytes was made at baseline and at 24 hours. Adverse events were recorded during the hospital stay and at follow-up visits.

Results: TURP and TUVP were both effective in producing a clinically important reduction in IPSS and positive change in the IPSS QoL question. The success rate for relief of symptoms was 85% for TURP and 74% for TUVP. Neither the success of the treatment nor the change in aggregated IPSS was significantly different between the groups. The improvement was sustained to 24 months after treatment with no significant difference between the groups. The effectiveness of both treatments was also equivalent when assessed through improvement in objective measures of urinary tract function, reduction in prostate size and the change in health questions of SF-36. The absolute incidence of adverse events was similar between the two groups. The incidence of severe or prolonged bleeding was less with TUVP, as evidenced by the need for blood transfusion and the drop in haemoglobin level 24 hours postoperatively. TURP and TUVP are broadly equivalent in direct NHS resource use. This study did not show any significant difference in inpatient stay or use of outpatient resources between the groups. The disposable electrodes used for TUVP are more expensive than reusable TURP electrodes.

Conclusions: TURP and TUVP are equivalently effective in improving the symptoms of benign prostatic

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enlargement over at least 2 years. TUVP is associated with less morbidity due to haemorrhage than TURP. Replacement of TURP by TUVP would not produce a significant cost benefit to the NHS unless a reduction hospital inpatient stay of at least 1 day could be secured. Further research is necessary to determine why patients stay in hospital after transurethral surgery to the prostate and how a reduction in the length of stay can be achieved. A much larger observational study/audit is required to assess the incidence of infrequently occurring adverse events after TUVP. Longer term follow-up is also needed.

Contents

List of abbreviations

BPH	benign prostatic hypertrophy
CI	confidence interval
CMG	cystometrography
CT	computed tomography
FBC	full blood count
HRQoL	health-related quality of life
ICS-BPH	International Incontinence Society – 'Benign Prostatic Hyperplasia'
IPSS	International Prostate Symptom Score
ITT	intention-to-treat
LRM	linear regression model
LUTS	lower urinary tract symptoms
MRI	magnetic resonance imaging
PROTO	Prostate Trials Office
PSA	prostate-specific antigen
PVR	post-void residual urine
QoL	quality of life
RCT	randomised controlled trial
SF-36	Short Form with 36 Items
TRUS	transurethral ultrasound of the prostate
TUIP	transurethral incision of the prostate
TURP	transurethral resection of the prostate
TUVP	transurethral vaporisation of the prostate
UTI	urinary tract infection

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

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Executive summary

Objectives

To compare and evaluate the clinical and cost-effectiveness of transurethral vaporisation of the prostate (TUVP), a new electrosurgical modality, with the standard treatment, transurethral resection of the prostate (TURP).

Design

A multicentre randomised controlled trial of pragmatic design with associated economic evaluation using cost minimisation.

Setting

Patients were recruited from four centres in south-east England.

Participants

Between March 1997 and August 1999, 235 men were recruited across the four participating centres. All patients had previously been assessed as requiring surgery for lower urinary tract symptoms deemed to be due to benign prostatic hypertrophy. Patients with clinical evidence of prostatic cancer, those unfit for surgery and those who had had previous prostatic surgery were excluded. Forty-five patients recruited were in urinary retention.

Interventions

Randomisation was performed by a sealed envelope system provided by the data monitoring team at PROTO. Symptomatic and retention patients were randomised separately to ensure an even distribution in each arm. Patients were randomised as close as possible to the time of their operation.

TURP was performed and subsequent management conducted according to the usual practice of the clinical team. TUVP was performed with the most promising available equipment using a technique described in the literature. Postoperative management after TUVP was left to the ward team, who were not necessarily informed to which treatment arm the patient had been allocated.

For the purpose of the study, patients were assessed clinically, by questionnaire and investigation at baseline, 2 months and 6 months after randomisation. A long-term follow-up postal questionnaire was sent to each patient at 2 years.

For the economic evaluation, direct costs from the NHS viewpoint were collected.

Main outcome measures

The International Prostate Symptom Score (IPSS) was used as the primary outcome measure. Patients in retention were allocated an IPSS related to the period immediately before retention occurred. A reduction of IPSS of ≥ 5 was taken as a satisfactory outcome. The IPSS quality of life (QoL) question provided disease-specific information about QoL.

The following were used as secondary outcome measures:

- urinary flow rate – two free flow rates with voided volume of >150 ml at each visit
- post-void urinary volume assessed by transabdominal ultrasound – two measurements at each visit
- prostate volume by transrectal ultrasound – at baseline and 6 months only
- pressure-flow urodynamics in the standing position using the medium fill rate technique
- questionnaires – SF-36, EuroQol and a sexual function section based on the International Incontinence Society – 'Benign Prostatic Hyperplasia' (ICS-BPH) questionnaire.

Blood was taken for measurement of full blood count and urea and electrolytes at baseline and at 24 hours. Adverse events were recorded on the Data Collection Form (DCF) during the hospital

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stay. At follow-up visits, any adverse event that had occurred since last contact with the study team was recorded, as were any visits to the district nurse, GP or any hospital.

Results

Effectiveness

TURP and TUVP were both effective in producing a clinically important reduction in IPSS and positive change in the IPSS QoL question. The success rate for relief of symptoms, defined as a >5 reduction in IPSS at 6 months was 85% for TURP and 74% for TUVP. Neither the success of the treatment nor the change in aggregated IPSS was significantly different between the groups. The improvement was sustained to 24 months after treatment with no significant difference between the groups. The effectiveness of both treatments was also equivalent when assessed through improvement in objective measures of urinary tract function, reduction in prostate size and the change in health questions of SF-36.

There was no change from baseline for other domains of SF-36 or EuroQoL.

Adverse events

For the purposes of this study, an adverse event was defined as any undesirable experience that the patient had, whether considered procedure-related or not.

The absolute incidence of adverse events was similar between the two groups. The incidence of severe or prolonged bleeding was less with TUVP, as evidenced by the need for blood transfusion and the drop in haemoglobin level 24 hours postoperatively.

Resource use

TURP and TUVP are broadly equivalent in direct NHS resource use. In particular, staff costs, theatre usage and capital equipment costs are the same. This study did not show any significant difference in inpatient stay or use of outpatient resources between the groups. The disposable electrodes used for TUVP are more expensive than reusable TURP electrodes.

Conclusions

The study's primary conclusions were as follows:

- TURP and TUVP are equivalently effective in improving the symptoms of benign prostatic enlargement.
- The improvement in symptoms lasts for at least 2 years.
- TUVP is associated with less morbidity due to haemorrhage than TURP.
- Reduction in bleeding after transurethral surgery to the prostate is not associated with a significant reduction in hospital stay when patients are managed by staff who are accustomed to managing patients after TURP.
- Replacement of TURP by TUVP would not produce a significant cost benefit to the NHS unless a reduction hospital inpatient stay of at least 1 day could be secured.

Recommendations for future research

The following areas of further research are recommended for consideration:

- Further research is necessary to determine why patients stay in hospital after transurethral surgery to the prostate and how a reduction in the length of stay can be achieved.
- A much larger observational study/audit is required to assess the incidence of infrequently occurring adverse events after TUVP. Until the results are available, TUVP should not replace TURP in the NHS.
- The patients in this study should be followed for a longer period to establish whether the durability of improvement is similar to 5 years and beyond.

Chapter 1
Introduction

The burden of disease

Benign prostatic hypertrophy (BPH) is a disease of elderly men. In 1990, the economic burden of BPH was estimated to be between £60 million and £91 million, representing 0.4% of total NHS expenditure.[1] This is despite the fact that only a small percentage of men with symptoms of BPH actually seek medical help. Britton and co-workers[2] reported that only 1% of patients per annum were referred to a urologist for BPH although the prevalence of symptoms consistent with BPH in the same group of men was between 26 and 57%. It seems likely that the economic cost of BPH will rise owing both to an increase in the number of older men and to an increasing demand for treatment.

Complications of transurethral resection of the prostate (TURP)

TURP is currently the most common surgical treatment for bladder outflow obstruction in NHS hospitals. Although the operative mortality associated with TURP has fallen and now stands at 0.1–0.25%[3] in elective patients, the morbidity of the procedure has remained stubbornly high at approximately 18%. The majority of the preoperative and early postoperative morbidity is attributable to bleeding, with 6.4% of patients requiring a blood transfusion. Other significant morbidity occurs from fluid absorption, TUR syndrome (2%) and urinary tract infection (14%).[4]

Late morbidity is even more common, with an incidence of retrograde ejaculation of 50–70%. Some 5–30% of patients with no antecedent history of impotence develop erectile dysfunction.[5] There has also been recent interest in orgasmic dysfunction after TURP[6] and its implications for patient treatment satisfaction. These problems, together with a drive for reduced inpatient stay and lower treatment costs, have stimulated the quest for safer, more cost-effective options for managing symptomatic BPH.

Alternatives to TURP

During the last decade, a variety of alternative treatment methods have been introduced, including watchful waiting, medical management using α-blockers or androgen suppression, insertion of prostatic stents and coils, balloon dilatation, prostatic hyperthermia and transurethral incision. Regrettably, none of these methods has proved superior in effectiveness to transurethral resection. The study described here is a contribution to the search for a safe and efficacious surgical alternative to TURP.

Electrosurgery to the prostate

Conventional electroresection as used in TURP is possible because the thin wire resectoscope loop concentrates radiofrequency alternating electrical current at the interface with the prostate tissue and causes heating of cells. The rapid delivery of energy results in boiling of intracellular water, forming steam which escapes, causing cellular disruption. The destructive effect is limited to a thin layer of cells and there is little dissipation of heat and little coagulation. The overall effect is therefore a pure cut. A combination of the rollerball and coagulating current produces slower energy transfer and therefore slower intracellular heating producing coagulation.[7]

Transurethral vaporisation of the prostate

Diathermy electrovaporisation of the prostate was described by Bush at a presentation to the Society of Minimally Invasive Therapy meeting in Berlin in 1993.[8] Bush's method, which he had used for more than a decade on more than 400 patients, involved loop resection of tissue after an initial diathermy vaporisation using a roller electrode with a cutting diathermy current of 250 W. In an unreported pilot study on 12 patients at The

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Royal London Hospital and St Andrew's Hospital in 1994–95, the lead investigator obtained good short-term results using a new electrode produced by Circon-ACMI and a diathermy output of 180 W. In this study of transurethral vaporisation of the prostate (TUVP), resection was not performed after diathermy vaporisation. There were no adverse effects and, because bleeding was minimal, the technique seemed to promise an opportunity to reduce hospital inpatient stay.

The primary aim of electrovaporisation is to produce both vaporisation and coagulation through the same electrode, thus preventing undue blood loss during tissue removal. This goal is achieved through the configuration of the electrode. TUVP roller electrodes have a number of ridges on which current is concentrated to produce tissue vaporisation together with flatter areas where current density is lower and coagulation can occur. As the electrode is passed over the prostate, the leading edge produces vaporisation and the trailing edge coagulates.

The extent of tissue removal has been measured by Narayan and colleagues,[9] who found that 3 mm of tissue was vaporised with an underlying 1-mm zone of coagulation. This work, together with that of Lim and co-workers,[10] analysed the different factors that affected the size and configuration of electrovaporisation lesions in an experimental setting. They found that the lesions produced depended on the nature of the electrode, the power settings of the electrosurgical generator, the electrosurgical generator itself, the speed of movement of the electrode, the downward pressure applied by the electrode and the impedance of the tissue. From this research, it was possible to improve the technique of TUVP. Optimum performance could be achieved through the use of new electrodes for each operation, more powerful electrosurgical generators with flat power-load curves, slower movement of the electrode over the surface and avoidance of excessive downward pressure.

Previous studies of TUVP

The first published data using the specifically designed Circon-ACMI Vaportrode™ electrode was presented by Kaplan and Te in 1995.[11] A subsequent study, by the same authors, involved 58 patients who underwent either TUVP or laser vaporisation of the prostate and found that TUVP was more effective in terms of both subjective and objective outcome measures.[12] The study was designed to assess the safety and efficacy of the new procedure and included monitoring of the rectal wall temperature in a small number of subjects. Other studies assessed the safety of TUVP with regard to bleeding, fluid absorption and thermal damage and found it to be at least as safe as conventional electroresection.[13,14] These early data were encouraging and there has been widespread acceptance of the new technique with very little additional scientific evaluation.

The literature on the subject continues to grow and more and more groups have published their clinical experience with the new technique, mainly in the form of prospective case series.[15–17] At the inception of this study, few investigators had attempted to produce a more rigorous appraisal of this procedure. Cetinkaya and colleagues[18] published a small randomised trial comparing TUVP with TURP. No pressure-flow urodynamic data were collected. A similar-sized study was also performed by Kupeli and co-workers.[19] Gallucci and colleagues[20] performed urodynamics and included transrectal ultrasound assessment of prostate volume to give an accurate picture of the effects of TUVP on the bladder outlet. This study did not include a control group, raising the possibility of selection bias. None of these studies was adequately powered to detect small differences in efficacy of the two study treatments.

The results of a number of randomised controlled trials (RCTs) of TUVP versus TURP have appeared in the literature since our study began. That of Shokeir and co-workers is another small in scale and conducted within a single unit.[21] The larger study of Hammadeh and colleagues[22] has shown that TUVP can be an effective and durable treatment with 2-year results equal to those of TURP.[23] However, this study was also performed in a single centre and therefore the generalisability of their results is uncertain.

The only multicentre RCT published to date is that of Galluci and co-workers,[24] who reported on a total of 150 patients. This study was conducted in nine centres in Italy with a maximum of 20 patients per centre. This could have led to difficulty in gaining adequate experience with the new technique of TUVP. It was not a pragmatic study but instead excluded patients on the basis of flow rates and prostate size. No patients in retention of urine were included. No power calculation was given and it seems unlikely that the numbers in this trial would allow more than an 80% power of detecting a 20% difference between the two groups. In addition,

data collection was incomplete in more than one-third of the patients operated upon.

Initial reports therefore suggest that TUVP and TURP are equivalently effective. TUVP does not provide material for histological examination but may be associated with less bleeding than TURP.

Hypotheses

The current study was conceived as a means to test the following linked hypotheses:

- TUVP is as effective as TURP in reducing lower urinary tract symptoms caused by BPH but has lower early morbidity.
- Because TUVP is associated with lower early morbidity, it should offer potential cost benefits for the NHS.

No single study has met all the criteria for a proper evaluation of TUVP. Evidence-based medicine requires more rigorous evaluation before a new technology can be recommended. This proof can best be obtained in an adequately powered, randomised, controlled trial – to date no such study has been performed.

Study design

This study was an evaluation of TUVP. It was a prospective, randomised, controlled, multicentre trial of TUVP against TURP. The clinical objective of the trial was to use a range of objective and subjective investigative tools to provide a broad analysis of the potential of TUVP as a treatment of bladder outlet obstruction due to BPH in the NHS as a whole.

Safety of any new procedure is obviously of paramount concern to the patient and to the NHS. The true incidence of complications for any procedure will only be determined when that procedure is applied widely to its intended population over a prolonged period. Small selected case series cannot give an accurate picture of the side-effect profile of TUVP.

A pragmatic trial is one in which the inclusion and exclusion criteria are such that the study population matches almost exactly that in which the operation will be performed on a routine basis. This trial, which was largely pragmatic in design, included a total of 235 patients. This should have allowed most common complications to be detected within this study, although many thousands of patients would be required to detect complications that occur with a frequency of $<1\%$.

Other aspects of safety in a modification of a TURP are important enough to require specific attempts to record their incidence. The major reported or projected advantage of TUVP over TURP is decreased blood loss. This study assessed blood loss indirectly by recording postoperative changes in haemoglobin and the number of units of blood transfused.

Cost analysis can take a number of different forms. The hypothesis for this thesis was that there would be no difference in treatment outcomes between TURP and TUVP. In this case a cost-minimisation analysis is appropriate.

Study administration

This study was set up in parallel with the Prostate Trials Office (PROTO), based at the Bristol Urological Institute under the direction of Professor Paul Abrams. PROTO was funded by a separate HTA Programme Project Grant but was charged with providing a Project Steering Group and data handling services for the project described here.

PROTO, its Clinical Trials Steering Group and its staff provided crucial input at several stages of the study. This included:

1. Steering Group
   (a) Modification and clarification of the initial trial design with a view to making the study more pragmatic in intent.
   (b) Identifying patient-based measures as the most important measures of outcome.
2. Statistical advice
   (a) The size of the study was reduced following discussions with Dr T Peters of PROTO.
3. Data handling
   (a) Generating and providing randomisation envelopes.
   (b) Receiving data collection forms, double data entry and checking data.
   (c) Data analysis and statistical testing
   (d) Generation of data reports to trial organisers.

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Chapter 2
Methods

Protocol

Planned study population

Men considered to require surgery for BPH were recruited from centres in the south-east of England. Of the four centres, two were in inner city London, of which one was a teaching hospital, Barts and The London NHS Trust, Whitechapel and the other was a district acute hospital, St Andrews Hospital, Bromley-by-Bow. The other two centres were in Slough, Berkshire and St Leonards, East Sussex. This mix of hospitals provided a heterogeneous group of patients whilst being geographically close enough to allow coordination between the centres without undue difficulty or expense. It could be argued that having all four centres in the south-east did not result in adequate diversity and that a wider dispersion of sites would allow greater generalisability within the NHS population. However, a number of ethnic minorities and a range of socio-economic groups were represented and we believe that the generalisability of our results should be adequate.

The aim was to recruit a study population that matched as closely as possible the characteristics of the patients who currently undergo TURP. Patients who were on the waiting list for surgery in the study centres were reviewed. If they fulfilled the inclusion criteria and were not obviously ruled out by the exclusion criteria, they were contacted by letter and asked if they would be interested in taking part in the study.

The inclusion and exclusion criteria are given below and were designed to maximise patient eligibility and thereby mirror the normal TURP population.

Inclusion criteria

- The patient should be a candidate for surgical treatment of bladder outlet obstruction.
- The patient must have completed pretreatment evaluation in accordance with currently accepted criteria for prostate surgery.
- The patient must be able to give written, informed consent to randomisation and treatment.

Exclusion criteria

- Any patient who has had previous bladder outlet surgery.
- Any patient with a physical status greater than ASA 3.
- Any patient with a clinically significant acute illness.
- Any patient taking medication that would, in the investigator's opinion, preclude entry into the trial.
- Any patient with known disease of the central or peripheral nervous system.
- Any clinical evidence of carcinoma of the prostate.

Patients known to match any exclusion criteria were automatically excluded and not approached. Those who failed to respond to the first letter were sent a second letter followed by a telephone call if there was still no response. If no telephone number was available then no further attempts were made to recruit those patients.

Patients who responded were invited to attend the Urology Department for a discussion with a member of the study team. At this meeting patients were shown a 10-minute videotape outlining the aims of the study and describing the two operations. After the video, patients were free to discuss any queries regarding the project. This was usually done in a group, following which patients were seen individually to assess their eligibility and discuss any further points of concern. At the end of the consultation, all patients were given a written information sheet about the trial that gave details of TUVP and TURP and the anticipated outcomes from treatment. The information sheet was submitted to and agreed beforehand by the Ethics Committee. The protocol clearly stated that patients would not be informed which treatment they had received until or unless their participation in the study came to an end. This was stated in the patient information document.

At this stage, the majority of patients felt able to say whether or not they were willing to participate in the study. Those patients who were recruited were given a date to return to the department for their baseline assessment. Patients who declined to

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TABLE I *Assessments after randomisation*

	MSSU	Bloods	Uroflow	PVR	TRUS	CMG	Questionnaire
Baseline	Y	Y	Y	Y	Y	Y	Y
24 hours	N	Y	N	N	N	N	Y
2 months	Y	Y	Y	Y	N	N	Y
6 months	Y	Y	Y	Y	Y	Y	Y
2 years	N	N	N	N	N	N	Y

participate were excluded and assured that this would not affect the timing of their own operation. Patients who felt unable to make a decision at this initial consultation were asked to telephone back once they had had an opportunity to discuss things with their partner or GP. GPs of participating patients were sent a letter informing them of their patient's decision and a copy of the trial information sheet that the patient had received. By recruiting from the waiting list, we hoped to ensure that all symptomatic patients were considered for enrolment into the study.

Summary of planned interventions and their timing

When patients had agreed to recruitment, they underwent baseline assessment. If they were admitted from a waiting list, the delay between recruitment and randomisation was governed by exigencies of the service. This delay varied from 1 week to several months. Patients in retention in those centres that proceeded to immediate surgery underwent randomisation comparatively promptly.

Randomisation was performed as close to the time of surgery as possible – while the patient was being anaesthetised in most cases. Patients then underwent either the study or control treatment.

Postoperative assessments were performed 24 hours, 2 months, 6 months and 2 years after randomisation. The component elements of these assessments are shown in *Table 1*. Abbreviations used in the table are defined in the text that follows.

Details of assessments

Blood tests (bloods)

Full blood count (FBC), blood urea and electrolytes were checked at each point. Prostate-specific antigen (PSA) was measured at baseline only.

Uroflow

Urinary flow rates were measured using a Dantec Urodyn 1000. Two free flow rates with voided volumes >150 ml were obtained at each visit. If patients were unable to void 150 ml then their results were included provided that the patient felt that it was a representative flow.

Post-void residual urine (PVR)

PVR volume was assessed by transabdominal ultrasound. Saggital and coronal images were obtained and the volume calculated using the equation for the volume of an elliptical spheroid ($0.52 \times \text{height} \times \text{length} \times \text{breadth}$). Two measurements were recorded on each visit.

Transurethral ultrasound of the prostate (TRUS)

Biplanar images of the prostate were obtained using a 7.5-MHz transrectal ultrasound probe. The volume of the prostate was calculated using the formula for an elliptical spheroid.

Cystometrography (CMG)

Pressure-flow urodynamics were performed with 8 Fr dual-lumen filling catheters and a separate rectal line. The test was conducted with patients in the standing position and medium-fill rates of 50 ml minute^{-1} were used.

Questionnaires

The questionnaire booklet included the International Prostate Symptom Score, Short Form with 36 Items (SF-36), EuroQol and a sexual function section based on the International Incontinence Society – 'Benign Prostatic Hyperplasia' (ICS-BPH) questionnaire.

Adverse events and resource usage

The following text is taken from the investigators' manual:

> "An adverse event was defined as any undesirable event experienced by the patient whether considered procedure-related or not.
>
> This includes, for example
>
> a) procedure related complications
>
> - bleeding requiring transfusion (irrespective of gland size)
> - return to theatre for any reason

- UTI/septicaemia/epididymo-orchitis
- prolonged catheterisation as a result of capsular perforation
- TUR syndrome
- change of catheter for blockage by chip or clot

b) procedure unrelated complications

- chest infection
- angina/MI
- DVT/PE

The above list is not exhaustive and investigators should use their own discretion when deciding when to complete an adverse event form."

In addition, a comprehensive range of specific perioperative complications were collected against a checklist. Postoperative complications suffered while the patient was in hospital were collected against a separate checklist.

After patients had left the hospital, any adverse event or use of NHS resources that had occurred since the last contact with the study team was identified by structured inquiry prompted by fields in the data collection form used at 2 and 6 months.

Details of planned interventions and rationale

Operative details

Operations were performed by eight consultants and four registrars. Only one surgeon had significant experience with electrovaporisation before the study began. A similar number of procedures in both groups were performed by consultants. American Society of Anesthesiologists (ASA) status was assessed by the senior anaesthetist present. Operation time was measured as the time from the positioning of the patient on the operating table to the time when the patient was transferred off the table. Antibiotic prophylaxis was given according to the policy of the operating surgeon.

An initial cystoscopy was performed in all cases and the prostate morphology recorded.

TURP was performed in the conventional manner using a Circon-ACMI 24.5 Fr continuous-flow resectoscope with a new wire loop for each patient. A Valleylab Force FX™ electrosurgical generator was used with settings adjusted according to the surgeon's preference; generally between 120 and 140 W Cut and between 50 and 60 W Coagulation. Each surgeon performed TURP to his normal extent and at the end of the procedure a three-way irrigating catheter was placed with either irrigation or a forced diuresis with frusemide in accordance with the operator's usual practice.

TUVP was performed using the same resectoscope and electrosurgical generator as for TURP. A new Circon-ACMI Fluted Vaportrode™ electrode was used for each patient. The generator was set at 180 W Cut and 55 W Coagulation in all patients. The operation was performed in a similar manner to conventional TURP until the surgeon felt that he had removed as much tissue as he would by TURP. A three-way irrigating catheter was inserted with irrigation or forced diuresis as necessary. In a subset of patients at one of the four study centres, expired breath alcohol readings were taken every 10 minutes during the operation using a Lion SD-2 Alcometer (Lion Laboratories, Barry, Wales, UK). The irrigating fluid at this centre was 1.5% glycine with 1% ethanol, whereas in the other three centres standard 1.5% glycine was used.

Any adverse event that occurred during the operation was recorded and the resectate specimen was weighed in theatre to the nearest gram.

Inpatient stay

After theatre, patients were admitted to the recovery area until their observations were stable, when they returned to the urology ward. Irrigation continued as required. Catheters were removed when the degree of haematuria permitted as assessed by the doctor attending the patient postoperatively. The patient's FBC and electrolytes were checked on the first postoperative day and a record of any blood transfusion was kept. The time and date of catheter removal were recorded and the success or failure of the trial without catheter was noted. The date of discharge was entered into the data collection form. Any missing data were retrieved from the patient's notes or the hospital Patient Administration System.

Details of patient assessment and rationale

Patients were assessed prior to operation and then again at 2 months, 6 months and 2 years after randomisation. The data were recorded on a collection form that was held by the principal site investigator. Once all data were complete, two copies of the data records were made. One copy was held locally, another was sent to the study coordinating team at The Royal London Hospital and the original record was sent to PROTO, Bristol, for creation of a computerised database and subsequent analysis.

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Primary outcome measures – patient-based outcomes

Symptom scores

Relief of symptoms is the primary determinant of success for most patients presenting with lower urinary tract symptoms (LUTS) due to BPH. In order to detect changes in symptoms, the instruments used must measure reliably their prevalence before and after any intervention – the instruments must be responsive enough to detect changes of the expected magnitude. In addition, if the instrument is to be used widely, it should combine consistency and sensitivity with brevity and ease of self-completion. The American Urological Association questionnaire[25] has been developed to measure LUTS in men with BPH and has been shown to be valid, reliable and responsive. The AUA-7 questionnaire has been adapted for use on a wider scale and forms the basis of the International Prostate Symptom Score (IPSS).

Symptom bother

Simply measuring the pattern and severity of LUTS does not provide a complete picture, especially when considering treatment. It is the bothersomeness of symptoms, rather than their mere presence or absence, which determines the patient's need for medical intervention. Elderly men can often tolerate a higher level of symptoms than younger men can because they have lower health expectations and can adapt their lifestyle to minimise the impact of LUTS. A number of questionnaires have been developed to assess symptom bother including the BPH-Impact Index and Symptom Problem Index.[26]

In a clinical trial, there is a limit to the amount of information which patients can reasonably be expected to provide. Beyond this limit patients may find the imposition too onerous and withdraw. There is said to be good correlation between the results of these disease-specific quality of life (QoL) questionnaires and the IPSS QoL question (Donovan J, PROTO, personal communication, 1996). A separate bother questionnaire has not been included and reliance has been placed on the responses to the single IPSS question.

Secondary outcome measures – subjective outcome measures of effectiveness

General health-related quality of life

Symptomatic BPH can interfere with QoL and overall health state in other ways than the prevalence and bother of symptoms. Pain, sleep, emotional well-being and ability to perform normal daily activities can all be affected by disease. A variety of instruments have been developed to measure such dimensions of health. The SF-36 questionnaire was developed for use in the Medical Outcomes Study[27] and has been validated in the UK by Brazier and colleagues.[28] It consists of 11 sections and addresses eight health dimensions: physical functioning, social functioning, role physical, role emotional, mental health, vitality, bodily pain and general health. There is also a question on change in general health. Each dimension is assessed in a number of questions and the responses are weighted and then expressed as a numerical score from 0 to 100. The SF-36 has been shown to discriminate between symptomatic and asymptomatic patients, stages and severity of disease and moderate treatment effects. One of the disadvantages of the SF-36 is the possibility of a floor effect in severely ill groups, whereby further deterioration from a low initial general health-related quality of life (HRQoL) status cannot be detected. This is unlikely to be of concern in men having bladder outflow surgery.

The EuroQol questionnaire contains two parts: a health status profile covering six domains and a visual analogue scale rating global HRQoL. It was developed for use in conjunction with other HRQoL measures and has the advantage of simplicity. However, its ability to detect minor or moderate changes in HRQoL is limited.

The combination of the SF-36 and EuroQol questionnaires should provide robust information on HRQoL and has been used in this study.

Sexual function

Sexual dysfunction is common after TURP. Retrograde ejaculation is the most frequent sexual complication and can be expected to occur in up to 80% of men undergoing this procedure. The effect on erectile dysfunction is less clear, but some authors suggest that between 5 and 30% of men will have an alteration in erectile function postoperatively. Sexual function has been shown to have an impact on patient assessment of treatment outcome and therefore rates of sexual dysfunction are an important consideration in assessing any new treatment.[2] At the time of inception of this study there was no validated questionnaire to assess the effect of surgery on sexual function. The ICS-BPH questionnaire included a section on sexual function and this was adapted with the addition of a question on orgasmic dysfunction.

Secondary outcome measures – objective outcome measures of effectiveness

Uroflowmetry

Uroflowmetry was developed in the 1950s by von Garrelts. The premise for the use of uroflowmetry

in the assessment of voiding is that flow rates reflect changes in resistance to flow through the bladder outlet. A number of methods have subsequently been developed to measure flow. The most basic of these is observation of the timed voided volume, but this provides no information on the pattern of flow.

The most commonly used machines in current practice rely on the impedance to a spinning disc caused by the urinary stream. This is then converted into an electrical signal by a transducer and displayed graphically. This allows changes in flow with time to be recorded and the recognition of different voiding patterns.

The advantages of measuring flow rates to assess outcome include the relative ease with which these measurements can be obtained and the non-invasive nature of the test. They are also objective in that they do not require any significant input by patient or physician and are measured on a continuous numeric scale. Uroflowmetry is not, however, without disadvantages. These include variation with voided volume, setting and number of measured voids. In addition, artefacts can be produced in the recording by 'wandering stream' and 'squeezing'. Despite these limitations, uroflowmetry has become a common and accepted method of assessing the bladder outlet and surgical interventions on it.

Post-void residual urine volume

Although uroflowmetry gives an indication of bladder outlet resistance, it gives no information on the effectiveness of bladder emptying. The assumption is that bladder outlet obstruction will initially be compensated by detrusor muscle hypertrophy with little change in either flow rates or bladder emptying. As resistance increases then the detrusor will decompensate and this will be evidenced by reduction in flow rate and less effective bladder emptying. High residual urine values predispose the patient to urinary tract infection (UTI) and stone formation and residual urine measurement has become an accepted indicator of the severity of bladder outlet obstruction. Residual urine measurement is most accurately performed by catheterisation of the bladder; however, this invasive method is neither acceptable to the patient nor practical in the urology clinic. Ultrasound assessment of residual urine volume has the advantages of being quick, non-invasive and easy to perform. The development of automated bladder scanners has meant that residual urine volume can be measured with a minimum of training.

The main disadvantage of ultrasound is that the volume is calculated on the basis of the bladder being an ellipsoid, which is a reasonable approximation but not absolutely accurate. However, given that there are wide variations in values of residual urine volume within individual patients, small inaccuracies are of little significance. Magnitude of residual urine does not, however, predict obstruction.[30]

Pressure-flow urodynamics

Flow rates and ultrasound assessment of the residual urine volume can give useful information on the bladder outlet. They cannot, however, define the presence or absence of obstruction since they are unable to distinguish between bladder outlet obstruction (BOO) and impaired detrusor function. This can only be achieved by the simultaneous measurement of both flow and detrusor pressure, otherwise known as pressure-flow urodynamics.

The routine use of this invasive technique in everyday urological practice is not widespread in the NHS. Men who are urodynamically obstructed have a better outcome following TURP than those who are not and, since the operation of TURP is primarily aimed at 'disobstruction' of the bladder, it is interesting from a research point of view to see if this aim is being achieved. This is not to say that operations on obstructed patients that do not disobstruct them but produce good symptom relief should be considered failures. Rather, it is an acceptance of the fact that we do not fully understand the mechanism of action of TURP.

Attempts have been made to overcome some of the drawbacks of conventional urodynamic studies by seeking to avoid catheterisation for pressure measurement. New techniques include the use of an inflatable cuff placed around the shaft of the penis to produce resistance to flow and measuring the maximum pressure that the detrusor can produce to overcome this resistance.[31] Such techniques remain experimental but may in future extend the application of pressure-flow measurement.

Prostate volume measurement

A few authors have suggested that prostate volume can be used as the sole diagnostic modality for BPH.[32] The volume of the prostate gland correlates poorly with the presence of symptoms.[33] However, it can predict the likelihood of complications such as acute urinary retention.[34] The effect of reduction of prostate volume is less clear; some authors have suggested that removing more tissue improves the outcome of TURP.[35] Open prostatectomy removed all of the enlarged

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adenomatous tissue leaving only the compressed prostatic tissue of the 'capsule'. TURP has been described as removing a similar amount of tissue to the open operation, although studies have shown that >50% of the gland remains behind even after a 'radical' TURP.[36] Nd:YAG laser ablation of the prostate removes very little tissue and yet the results of these three different operations are similar in terms of symptom relief and flow rate improvement. There is therefore little to be gained from the routine measurement of prostate size reduction after surgery, although it may be that tissue removal might predict longevity of effect.[37]

In order to examine this hypothesis further, accurate measurement of prostate volume pre- and postoperatively is required. Prostate volume can be measured in a number of ways, including ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI). The availability and acceptability of ultrasound make it the most widely used. Ultrasound of the prostate can be performed both transabdominally and transrectally; however, studies have shown the transrectal approach to be more accurate. Planimetry is the best method of measuring volume but it is time consuming and is therefore not routinely used. An adequate estimation of volume can be obtained by measuring the three dimensions of the prostate and using the formula for the volume of an ellipsoid: $0.52 \times \text{height} \times \text{width} \times \text{length}$. Calculations have shown that this value will differ from that obtained by planimetry by 10–15% – an acceptable margin of error for the time saved.[38]

Sample size

The IPSS score was used as the primary outcome measure since patients present with symptoms and it is the relief of these symptoms with which they are most concerned. Patients presenting in retention were allocated an IPSS score on the basis of their recollection of symptoms in the week leading to the episode of retention. A reduction in IPSS score of ≥ 5 points was taken to indicate a successful outcome. This magnitude of difference is readily discernible to the patient according to Barry and colleagues.[39] By defining success in this way, we could reasonably expect TURP to have a success rate of 85%. In order to detect a difference of 15% with an 80% power at the 5% level required 220 patients. Assuming a drop-out rate of 10% then approximately 240 patients needed to be recruited (calculated by Dr T Peters, PROTO).

The secondary objective measures of outcome have little direct relevance to the patient. The hypothesis to be tested by this study was that the interventions were equivalent. Statistically significant differences in these measures might challenge this assumption without having clinical relevance.

The study was powered to detect differences in effectiveness. Very much larger numbers would be required to identify uncommon adverse events (<1% incidence).

Statistical analysis

All comparative analyses were completed on an intention-to-treat (ITT) basis.

Completed data collection forms were sent to PROTO. All data were entered on to a Microsoft Access database. Double data entry was performed and any discrepancy checked against the original form or discussed with the investigative team. Dr Q Yang supervised the database.

Data were transferred from the database into STATA version 6.0 (STATA, College Station, TX, USA) for further analysis. Data were plotted graphically using STATA to assess normality of distribution. Parametric data were analysed using Student's *t*-test. Non-parametric data were analysed using the Wilcoxon signed-rank test and Wilcoxon rank-sum test. The χ^2 test was used for proportions. In comparing the effects of the two treatments with each other, a general linear regression model was used where appropriate. In those instances where the linear regression model was not appropriate, the analysis was made by comparing the results of the treatments at each follow-up point and by comparing the extent of the improvement from baseline in each group. Results were taken as statistically significant with a *p*-value of <0.05.

Data adjustment rule for IPSS scoring

IPSS is calculated as the sum of seven individual scores (1–5) from seven questions. Not all forms were fully completed. A data adjustment rule was applied to IPSS scores throughout the study.

The data adjustment was as follows:

- If two question scores were absent, they were replaced by values equivalent to the five available scores, that is, the average of the five available scores was used for the other two values.
- If more than two question scores were absent, the IPSS was considered as missing data.

Assignment

Masking and randomisation process

Individual patients were randomised via a sealed envelope system. Each envelope contained a paper slip allocating the patient to either TURP or TUVP. A random number-generating computer program at PROTO generated the sequence of the operations. Each centre had its own group of opaque envelopes containing a slip of paper indicating the allocation. The outside of the envelopes was numbered in sequence by PROTO. Symptomatic and retention patients were randomised in a separate sequence to ensure an even distribution in each arm. Patients were randomised as close as possible to the time of operation and preferably whilst in the anaesthetic room. The randomisation slip was stapled to the patient record form.

Consideration was given to a telephone randomisation system that would have been provided by the PROTO. This represented the ideal situation as it reduced the potential for any allocation bias. Unfortunately, this service could not be provided from the start of the trial and there were practical problems with early theatre starts and late finishes which would have necessitated randomisation outside normal office hours.

Randomisation was stratified by centre and by symptom/retention. Treatment allocations were by permuted blocks.

Blinding

In trials of surgical treatments, it is clearly not possible to have a crossover between the two arms, nor is it possible to blind the surgeon to the technique being used. It is sometimes feasible to blind the investigators who are assessing the patients and the patients themselves. In our study we did not inform the patients which operation they received either pre- or postoperatively. All patients were returned to the ward with a three-way catheter and irrigation *in situ*.

The medical and nursing staff looking after the patient were usually not directly involved in the study and decisions on discharge and catheter removal were made in the normal manner. However, our study was not truly single-blind for a number of reasons: patients may have watched their operation on the monitor if having a spinal anaesthetic, and the type of operation performed was written in the patient's records and could therefore be read by anyone on the ward. The main investigators were intimately involved in both the randomisation process and the follow-up of patients. Data analysis was performed by a separate team at PROTO geographically separated from the trial sites.

Economic evaluation

Costs were collected from the NHS viewpoint and only direct costs were collected. An initial pilot study was conducted to determine which factors were discriminatory between the two treatment arms. Data that were not likely to be systematically different, such as the use of prophylactic antibiotics, were not collected. In all patients the duration of hospital stay, time in theatre and blood transfusion requirement were recorded. Common complications were identified and costed through the adverse event report form. Details of postoperative GP and hospital visits were recorded at the 2- and 6-month interviews. Analysis was performed on an ITT basis.

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Chapter 3
Results

Participant flow and follow-up

See the flow diagram in *Figure 1*.

Analysis

Study population

A total of 455 patients were approached between March 1997 and March 1999 and 235 patients were recruited. A total of 1759 patients underwent transurethral surgery to the prostate during this time at the four centres. This means that the patients recruited to the study represented only 13% of all patients. This figure seems rather low but is in line with figures from other large-scale trials and difficulties experienced by other investigators in the same field.[40] Of the 220 men considered but not randomised, 33 were unsuitable because they contravened exclusion criteria and 157 declined to be randomised or withdrew consent. No explanation was sought from men who declined to be randomised. The reasons why the remaining 30 men did not take part were not recorded.

In one of the centres, patients in acute retention of urine were discharged with a catheter and placed on the waiting list for operation, allowing these patients to be readily identified. In the other three centres, patients with acute retention were admitted as emergencies and had their operations performed during their initial admission. These patients proved difficult to recruit for a number of reasons: clinicians did not refer them to the trial team, there was a short window of opportunity for recruitment prior to operation and study resources were not located on the site of these emergency admissions. Patients admitted as an emergency were less interested in or less able to comprehend the study's aims and design. This may have been due to the sudden change in their health or anxieties regarding their treatment that made them less willing to participate in anything experimental. These difficulties meant that only 45 (19%) of the total of 235 patients recruited were in acute retention. This figure is somewhat less than the 28% quoted in the National Prostatectomy Audit.[5]

The distribution of randomised patients between the contributing centres is shown in *Table 2*.

Randomisation validity

A total of 235 men were randomised, 120 to TURP and 115 to TUVP.

Of the 235 men randomised, 190 were symptomatic and 45 were in urinary retention. One hundred symptomatic men were randomised to TURP and 90 were randomised to TUVP. Twenty men in retention were randomised to TURP and 25 were randomised to TUVP.

The groups were alike in self-determined ethnicity and ASA status (*Tables 3* and *4*).

There was no significant difference between the groups for any baseline measurement (*Table 5*).

Primary outcome measure: data quality at baseline

The primary outcome measure is change in the IPSS. IPSS data collection forms for 12 men (six TURP, six TUVP) were either blank or missing at baseline. Nine of these patients were in retention and should have been assigned an IPSS based on symptoms suffered before retention. Since the

TABLE 2 *Distribution of patients between centres by group*

Contributing centre	Symptomatic	In retention	Total no. of patients (%)
Royal London	53	14	67 (28.5)
Conquest Hospital, Hastings	59	21	80 (34.0)
Wexham Park, Slough	63	2	65 (27.7)
St Andrew's, Bow	15	8	23 (9.8)
Total	190	45	235 (100)

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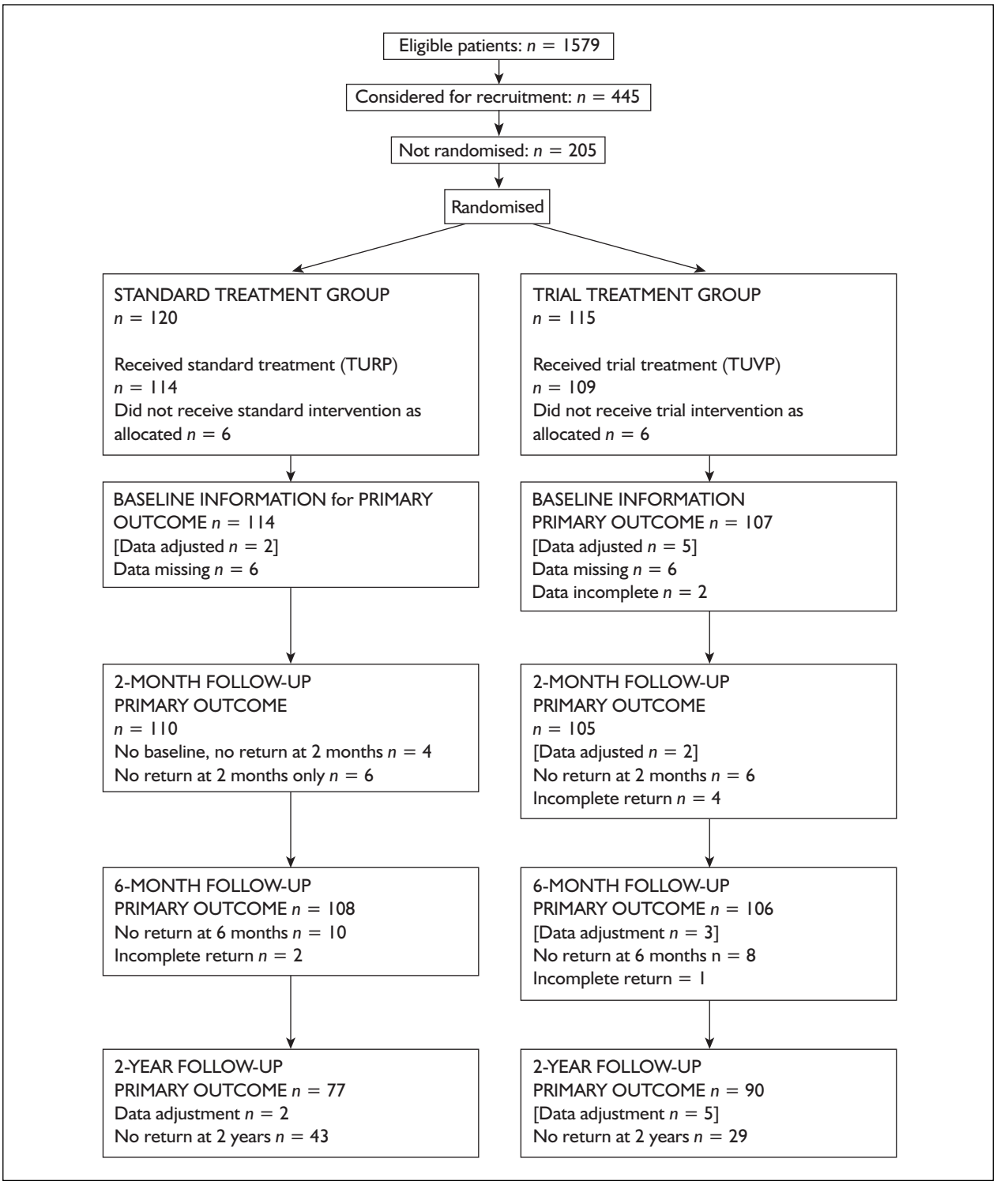

FIGURE 1 *Trial flow diagram*

forms were missing or blank, the data were counted as missing data. The three sets of missing data for symptomatic patients were lost through collection error.

Operation of the data adjustment rule is noted in the data flow diagram.

There was no difference in IPSS between the groups at baseline (*Table 6*).

*Effect of intervention on primary outcome measure (IPSS) (***Table 7***)*

The assumption made in the power calculation was that TURP could be expected to be successful

TABLE 3 *Self-described ethnicity by group*

Ethnic group	TURP	TUVP	Total
White	112	101	213
Afro-Caribbean	1	3	4
Black British	1	3	4
Indian	3	2	5
Pakistani	0	1	1
Bangladeshi	0	2	2
Chinese	3	2	5
Other	0	1	1
Total	120	115	235

TABLE 4 *ASA status recorded by senior anaesthetist present*

Status	TURP	TUVP	Total
ASA 1	45	43	88
ASA 2	50	51	101
ASA 3	13	9	22
Total	108	103	211

TABLE 5 *Baseline measurement means by group*

	TURP	TUVP
Age (years) (*n*)	69.7 (120)	70.2 (115)
IPSS (*n*)	20.7 (114)	20.7 (107)
Q_{max} (ml s^{-1}) (*n*)	10.5 (97)	10.1 (94)
PVR (ml) (*n*)	171 (94)	181 (91)
VV (ml) (*n*)	245 (97)	244 (94)
TRUS (ml) (*n*)	51.1 (103)	54.3 (100)
PSA (*n*)	4.6 (99)	4.7 (101)
Serum creatinine (mmol l^{-1}) (*n*)	104 (106)	105 (100)

VV, voided volume.

in reducing IPSS by ≥ 5 points in 85%. In the case of TURP, this is borne out by the results showing that the target percentage was reached at 6 months and 2 years. The target percentage was not reached during the course of the study in patients who underwent TUVP. However, at no stage did the difference between the success rate in the TURP and the TUVP groups reach the 15% level that the study was powered to detect. Using a 5-point improvement in IPSS as the criterion of success, we conclude that there is no significant statistical difference between the groups. It is of interest, however, that a group of patients undergoing TUVP showed a negative change in IPSS, that is, their symptoms were worse after surgery. This effect of TUVP was sustained out to 2 years follow-up and accounted for about 15% of the study group. By contrast, very few patients noted a deterioration in symptoms after TURP at any stage postoperatively and no patients were represented in this group at 2 years.

The aggregated IPSS data for each group at baseline, 2 months, 6 months and 2 years are shown in *Table 8*.

Results of normality tests suggest that the IPSS scores were not normally distributed in either the TURP or the TUVP group. Non-parametric statistical analysis (Wilcoxon signed-rank test) demonstrated a highly significant change in IPSS after both interventions maintained through all post-operative data points.

At 2 and 6 months, the data do not meet the assumptions for the linear regression model (LRM) method while taking the baseline level as covariate. Even when the score at follow-up was adjusted for baseline, the residuals remained insufficient to permit valid analysis by the LRM method. Therefore, we carried out two different tests for comparison. First, a two-sample Wilcoxon rank-sum (Mann–Whitney) test, used to compare the IPSS between the two treatment groups **regardless of the baseline level**, showed a significant difference in favour of TURP at 2 months after randomisation. This significant difference had disappeared by the 6-month data point. The difference at 2 months did not reach the 5 points deemed necessary for patients to recognise a clinical difference between symptoms (5 is readily appreciated, 0–2 are not).

The normality tests suggested that the **change** in IPSS between baseline and the 2- and 6-month data points are normally distributed. Even when the score at follow-up was adjusted for baseline, the residuals remained insufficient to permit valid analysis by the LRM method. The second method applied to these data was a two-sample *t*-test to compare the **change** in IPSS from baseline between two treatment groups. The results showed that at 2 and 6 months, the interventions had both achieved an equivalent **change** in IPSS.

A comparison of the outcome of the interventions at 24 months was valid using the LRM method with baseline IPSS as covariate. There was no statistical difference in IPSS between the groups. *Table 9* records the estimated difference in IPSS between the groups and its confidence intervals.

It was concluded that TURP and TUVP produce a statistically and clinically equivalent improvement in IPSS that is sustained to 2 years after randomisation.

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TABLE 6 *Primary outcome measure at baseline*

	TURP (*n* = 114)	**TUVP (*n* = 107)**	**Total (*n* = 221)**
Mean IPSS	20.7 SD = 6.9 95% CI: 19.4 to 22.0	20.7 SD = 7.3 95% CI: 19.3 to 22.1	20.7 SD = 7.1 95% CI: 19.8 to 21.6

CI, confidence interval; SD, standard deviation.

TABLE 7 *'Successful' treatment at 2 months, 6 months and 2 years by modality*

Change in IPSS	**TURP group**			**TUVP group**		
	2 months (*n* = 105)	**6 months (*n* = 103)**	**2 years (*n* = 75)**	**2 months (*n* = 101)**	**6 months (*n* = 100)**	**2 years (*n* = 84)**
>5	81 (77.1%)	88 (85.4%)	63 (84%)	68 (67.3%)	74 (74%)	62 (73.8%)
>0–5	12 (11.4%)	11 (10.7%)	8 (10.7%)	12 (11.9%)	11 (11%)	5 (5.9%)
0	2 (1.9%)	1(1%)	4 (5.3%)	4 (4%)	1 (1%)	5 (5.9%)
<0	10 (9.5)	3 (2.9%)	0	17 (16.8)	14 (14%)	12 (14.3%)

n = Number of paired data available.

TABLE 8 *Change in IPSS after intervention by intervention type*

Data point	**TURP**				**TUVP**			
	n	**Mean**	**SD**	**95% CI**	***n***	**Mean**	**SD**	**95% CI**
Baseline	114	20.7	6.9	19.4 to 22.0	107	20.7	7.2	19.3 to 22.1
2 months	110	9.8	7.2	8.4 to 11.1	105	11.8	7.7	10.3 to 13.3
6 months	108	6.9	5.5	5.8 to 7.9	106	8.5	7.4	7.1 to 10.0
2 years	77	7.5	5.8	6.2 to 8.8	90	8.6	7.2	7.1 to 10.1

TABLE 9 *Estimated difference in IPSS between TURP and TUVP groups*

Data, point	**Difference in IPSS between TURP and TVP groups**		
	n	**Estimated difference in IPSS scores**	**95% CI**
Baseline	221 (114/107)	0.03	–1.84 to 1.92
2 months	215 (110/105)	–1.99	–4.00 to 0.01
6 months	214 (108/106)	–1.65	–3.41 to 0.11
2 years	167 (77/90)	–1.06	–3.10 to 0.97

TABLE 10 *Change in IPSS QoL question after intervention by intervention type*

Data point	TURP				TUVP			
	n	Mean	SD	95% CI	*n*	Mean	SD	95% CI
Baseline	114	4.9	0.98	4.7 to 5.0	109	4.6	1.17	4.4 to 4.8
2 months	109	2.3	1.73	2.0 to 2.7	105	2.6	1.82	2.2 to 2.9
6 months	108	1.6	1.34	1.4 to 1.9	107	2.0	1.63	1.6 to 2.2
2 years	80	1.8	1.34	1.4 to 1.2	89	1.9	1.62	1.3 to 2.0

TABLE 11 *Change in EuroQoL scores*

Data point	TURP				TUVP			
	n	Mean	SD	95% CI	*n*	Mean	SD	95% CI
Baseline	116	0.74	0.25	0.68 to 0.78	112	0.78	0.23	0.73 to 0.82
2 months	110	0.75	0.26	0.79 to 0.80	108	0.79	0.25	0.74 to 0,84
6 months	108	0.79	0.24	0.74 to 0.83	105	0.77	0.28	0.71 to 0.82
2 years	82	0.74	0.25	0.69 to 0.80	90	0.78	0.27	0.72 to 0.83

TABLE 12 *Change in EuroQoL health scale scores*

Data point	TURP				TUVP			
	n	Mean	SD	95% CI	*n*	Mean	SD	95% CI
Baseline	116	71.3	17.6	68.1 to 74.6	109	75.8	16.0	72.7 to 78.8
2 months	108	71.4	18.9	67.8 to 75.0	107	77.2	16.1	74.2 to 80.3
6 months	109	72.9	18.3	69.4 to 76.4	108	76.9	19.4	73.2 to 80.6
2 years	77	70.4	19.5	66.0 to 74.9	87	75.6	20.1	71.3 to 79.9

Disease-specific quality of life question (IPSS QoL question)

The results of the IPSS QoL question are given in *Table 10*. The data are shown to be severely skewed from normality so non-parametric analyses were employed. The Wilcoxon signed-rank test showed a significant difference to the IPSS QoL assessment that was sustained to 2 years from randomisation. The improvement at all data points was similar in both groups. We conclude that TURP and TUVP produce a significant improvement in IPSS QoL score that is sustained to 2 years from randomisation.

Effect of intervention on secondary outcome measures – subjective outcome measures of effect

General health-related quality of life (EuroQoL)

There was no difference between baseline EuroQoL scores and scores at all points after randomisation (*Table 11*).

On the second part of the EuroQoL questionnaire, the man is asked to mark a level on a 1–100 analogue scale to indicate health status, where 100 indicates perfect health. There was no significant change at any data point (*Table 12*).

Similarly, there was little or no change in domains of the SF-36 and no significant difference between the two groups in this respect. These data are available if required.

We conclude that any change in general HRQoL result from either intervention is not detectable by EuroQoL or SF-36.

Sexual function

Erectile dysfunction

The rate of drop-out for the sexual function question was high (*Table 13*). Only 143 men (60.9%) in the trial provided information at all data points. There was no significant change in the percentage of men suffering erectile dysfunction between baseline and 2 years after randomisation.

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TABLE 13 *Erectile dysfunction after intervention*

Data point	TURP				TUVP			
	Normal (%)	ED (%)	Missing	Total	Normal (%)	ED (%)	Missing	Total
Baseline	62 (56.4)	48 (43.6)	10	120	75 (68.8)	34 (31.2)	6	115
2 months	64 (62.8)	38 (37.2)	18	120	68 (66.0)	35 (34.0)	12	115
6 months	62 (61.4)	39 (38.6)	19	120	65 (66.3)	33.7 (33.7)	17	115
2 years	43 (59.7)	29 (40.3)	48	120	58 (69.1)	26 (30.9)	31	115

ED, erectile dysfunction.

TABLE 14 *Erectile dysfunction in men with normal sexual function before surgery*

Data point	TURP	TUVP
2 months	4/59 reported ED	11/70 reported ED
6 months	5/58 reported ED	12/69 reported ED
2 years	8/43 reported ED	12/64 reported ED

A comparison of the number of men who had had normal sexual function who became impotent at 2 years (*Table 14*) showed no significant difference between the two groups at any data point using the χ^2 test.

Failed ejaculation

About one-third of men in both groups reported no ejaculation before surgery to the prostate. The rate of ejaculatory dysfunction after surgery was increased by approximately 25%. There was no significant difference between the groups (*Table 15*).

Secondary outcome measures – objective outcome measures of effectiveness

*Maximum urinary flow rate (***Table 16***)*

Forty-four patients (39 of them in retention) did not provide baseline Q_{max}, PVR volume or voided volume data. Six patients provided baseline data before going into retention. Data were fairly close to a normal distribution. Both TURP and TUVP produced a highly significant change in Q_{max} at 2 and 6 months from randomisation using a paired *t*-test. A two-sample *t*-test suggested that there was no significant difference between TURP and TUVP in either Q_{max} or change in Q_{max} from baseline.

*Post-void residual volume (***Table 17***)*

Using the Wilcoxon signed-rank test for non-parametric data, it was clear that both treatments produced a significant improvement in PVR volume at both 2 and 6 months; $p < 0.0001$. Comparison between the two arms with a two-

TABLE 15 *Change in ejaculatory function*

Data point	TURP				TUVP			
	Normal (%)	Failed ejacul (%)	No ejacul (%)	No data	Normal (%)	Failed ejacul (%)	No ejacul (%)	No data
Baseline	65 (64.4)	2 (2.0)	34 (33.6)	19	70 (68)	3 (2.9)	30 (29.7)	12
2 months	34 (34.0)	23 (23.0)	37 (37.0)	20	34 (36.2)	23 (24.4)	37 (39.4)	21
6 months	35 (35.7)	23 (23.5)	40 (40.8)	22	37 (40.2)	19 (20.7)	36 (39.1)	23
2 years	31 (45.6)	15 (22.1)	22 (32.3)	52	36 (43.4)	16 (19.3)	31 (37.3)	32

TABLE 16 *Change in Q_{max}*

Data point	TURP				TUVP			
	n	Mean	SD	95% CI	*n*	Mean	SD	95% CI
Baseline	97	10.52	5.04	9.5 to 11.5	94	10.10	4.35	9.2 to 11.0
2 months	111	21.23	10.20	19.3 to 23.1	108	19.12	11.76	16.9 to 21.4
6 months	109	22.29	10.25	20.3 to 24.2	109	19.6	11.04	17.5 to 21.7

TABLE 17 *Change in post-void residual volume*

Data point	TURP				TUVP			
	n	**Mean**	**SD**	**95% CI**	***n***	**Mean**	**SD**	**95% CI**
Baseline	94	170.8	184.3	133.1 to 208.6	91	181.1	162.4	147.3 to 214.9
2 months	110	77.8	120.7	55.0 to 100.6	109	59.3	59.5	47.8 to 70.8
6 months	109	71.8	87.4	54.7 to 87.8	109	71.0	72.0	57.3 to 84.7

TABLE 18 *Reduction in prostatic volume*

	TURP (range) (*n* = 98)	**TUVP (range) (*n* = 97)**
Reduction in prostatic volume (ml)	24.8 (19.9–29.7)	21.5 (16.8–26.2)
Reduction in prostatic volume (%)	40.5 (34.1–46.9)	36.2 (30.2–42.3)
Resectate weight (g)	19.5 (16.8–22.2)	N/A

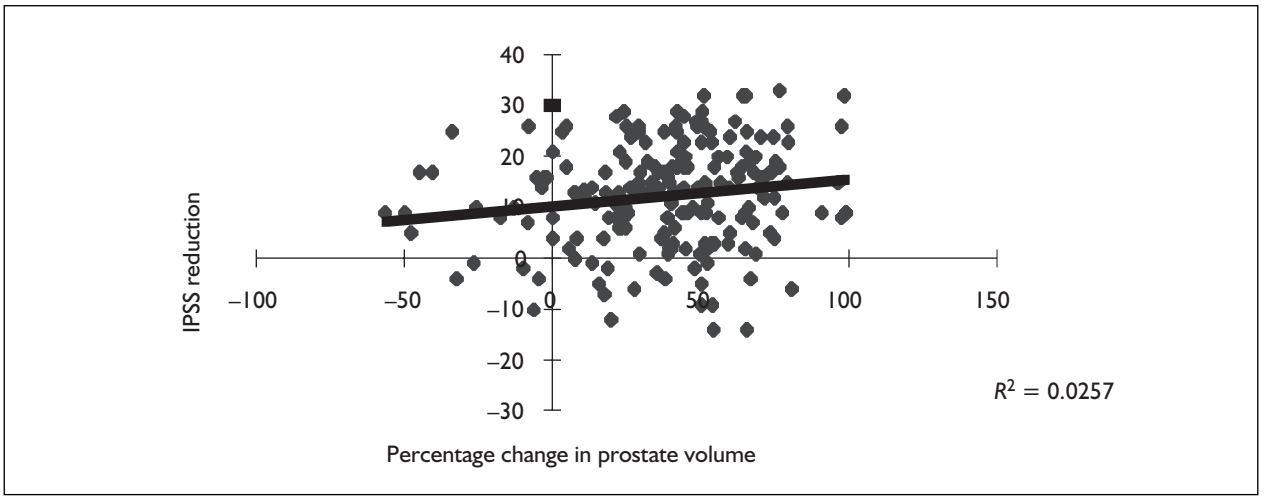

FIGURE 2 *Percentage change in prostatic volume against improvement in IPSS score*

sample Wilcoxon rank-sum test confirmed no statistically significant difference in either overall values or reduction in PVR volume.

*Prostatic volume (***Table 18***)*

A total of 103 patients from the TURP group had TRUS measurement of prostatic volume at both baseline and at 6 months follow-up; 100 TUVP patients had both measurements. Results showing an increase in prostatic size ($n = 9$) were excluded. There was no significant difference between the reduction in prostatic volume or the percentage reduction in prostatic volume between the two groups.

When percentage prostatic volume removal is plotted against improvement in IPSS and Q_{max} (*Figure 2*), the Pearson correlation coefficient is low (0.019–0.026). This suggests only a very weak association between the volume of tissue removed and the subjective outcome of prostatic surgery.

Pressure-flow urodynamics

Urodynamic studies were not performed on patients in retention at baseline. In total 74 patients did not have urodynamics either at baseline or at 6 months (34 TURP, 40 TUVP). A further 51 men declined repeat urodynamics at follow-up. Three patients had no baseline urodynamics but consented to follow-up assessment. Consequently, 97 patients had data available from both time points.

Both treatments have a comparable similar urodynamic outcome (*Table 19*).

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TABLE 19 *Urodynamic outcome of TURP and TUVP*

Procedure	Baseline	6-month follow-up			
		Obstructed	Equivocal	Unobstructed	Total
TURP	Obstructed	7	8	15	30
	Equivocal	5	7	6	18
	Unobstructed	1	2	3	6
	Total	13	17	24	54
TUVP	Obstructed	9	3	20	32
	Equivocal	0	3	4	7
	Unobstructed	0	0	4	4
	Total	9	6	28	43

TABLE 20 *Details of intraoperative adverse events*

Adverse event	TURP (n = 120)	TUVP (n = 115)
Total patients	11	13
Heavy bleeding	7	1
Perforation	4	6
Cardiovascular problem	1	1
Other	1	5

TABLE 21 *Outcome of trial without catheter*

	TURP	TUVP
Successful 1st TWOC	109	87
Successful 2nd TWOC	3	16
Successful 3rd TWOC	3	3
Successful 4th TWOC	1	1

TWOC, trial without catheter.

Adverse events

Intraoperative adverse events

In the TURP group, 11 patients experienced 13 complications. In the TUVP group, 13 patients had 13 adverse events. The most common complication was capsular perforation, which in no case led to perceptible clinical problems. Details of the adverse events are given in *Table 20*. There was no statistically significant difference in the overall frequency of intraoperative complications between the two groups (p = 0.60). There appears to be a strong trend of difference between groups in the incidence of heavy bleeding, but a two-tailed Fisher's exact test gives p = 0.06, which marginally misses the significance cut-off point of 0.05.

Perioperative blood loss

A total of 103 patients in the TURP arm and 99 patients in the TUVP arm had paired data on haematocrit and haemoglobin pre- and postoperatively. The mean change in haematocrit was 0.039 [95% confidence interval (CI) 0.031 to 0.046] for the TURP arm compared with 0.023 (95% CI 0.016 to 0.030) for TUVP. The mean change in haemoglobin was 1.2 g dl^{-1} (95% CI 0.9 to 1.4) for TURP and 0.6 g dl^{-1} (95% CI 0.4 to 0.8) for TUVP. This difference is highly significant (p = 0.003).

Nine patients who underwent a TURP required a blood transfusion compared with two in the TUVP group. No patient required more than six units of blood. Using the χ^2 test, there is a statistically significant difference in the need for blood transfusion between the two groups (p = 0.04) even when randomised on an ITT basis.

One of the patients who received a blood transfusion in the TUVP group had actually undergone TURP through operator error, therefore the true incidence of blood transfusion in TUVP was one out of 115 patients.

Duration of catheterisation

The duration of catheterisation was taken as the time from the end of operation to the time of successful catheter removal. A total of 116 TURP patients had complete data regarding catheterisation compared with 107 TUVP patients. The number of times that a trial without catheter was performed is given in *Table 21*.

Five patients had catheterisation times in excess of 50 days (range 52–255 days). All of these patients had presented in retention and had undergone TUVP. Two of these patients had presented in chronic retention and had prostate volumes >100 ml.

The mean duration of catheterisation in the TURP arm was 3.1 days (95% CI 2.3 to 3.9) as against 4.9 days (95% CI 2.7 to 7.1) for TUVP. However, this

TABLE 22 *Histological details of patients found to have prostate cancer*

Histology details	Trial number	Preoperative PSA
Gleason sum 3	21003	3.9
Well-differentiated adenocarcinoma	21014	4.5
Gleason sum 9	22017	15
Gleason sum 7	32005	18.8
Gleason sum 3	41038	2.8
Gleason sum 2	41041	5.6

was not statistically significant ($p = 0.93$). Taking the symptomatic and retention patients as a whole, there was a statistically significant difference ($p = 0.001$) in catheterisation time: 2.7 days (95% CI 2.2 to 3.3) versus 9.2 days (95% CI 3.6 to 14.7). In addition, there was a significant difference between the four centres with a range of mean catheter duration of 2.2–5.3 days, suggesting that there may be some centre effect.

Inpatient stay

This information was available in all but three patients. The mean duration of stay was 4.6 days (95% CI 3.9 to 5.4) in the TURP arm and 4.4 days (95% CI 3.8 to 5.1) for TUVP patients. The difference in mean hospital stay did not reach statistical significance ($p = 0.47$). The data distribution was severely skewed and the median duration of hospital stay was 4 days in the TURP group and 3 days in the TUVP group.

Ten patients had a total inpatient stay of at least 10 days (range 10–32 days). All but one of these patients was admitted in retention and three patients waited more than 1 week for theatre time to become available. Three of the patients received TURP and seven TUVP. If these patients with exceptionally long hospital stays are not included in the analysis, then the mean duration falls to 4.0 days for TURP and 3.8 days for TUVP. Overall, 60% of TURP patients and 70% of TUVP patients stayed in hospital for ≤ 4 days.

Histology results

TURP specimens were sent to the laboratory for histological analysis in the normal manner. No specimens were available in the TUVP group. All 120 TURP cases had confirmed histology results. Six patients had histologically confirmed evidence of carcinoma of the prostate, as shown in *Table 22*.

Two of the six presented in retention and had preoperative PSA results of 15 and 18.8. The other four patients had preoperative PSA values between 2.8 and 5.6.

Economic evaluation

The clinical outcomes of the two treatments were identical and therefore a cost-minimisation analysis was performed.

Resource use

There was no statistically significant difference between TUVP and TURP in any of the major variables affecting cost. The amount of theatre time, staff mix involved and the length of hospital stay were equivalent in both arms. The complication rate was similar in both arms although the blood transfusion rate was higher with TURP at 8%. This was offset by the lower cost of the loop electrode and more successful first removal of catheter. The number of general practice attendances in the first 6 months after surgery was similar in both groups, 61 for TURP and 69 for TUVP. Eighteen of the 61 general practice visits by the TURP patients were considered by the investigators to be related to the operation compared with 27 of the 69 visits in the TUVP arm.

TUVP, unlike many other alternatives to TURP, does not require a large capital outlay, although a modern electrosurgical generator is beneficial. There is a difference in the cost of the electrodes: a conventional loop cost £95 in 1996 compared with £160 for the Circon-ACMI Fluted Vaportrode™. Although the vaportrode is clearly marked for single use, most urologists treat standard resectoscope loops as reusable items. If resectoscope loops are used as single-use items as the manufacturers recommend, there is a cost saving of £65 per patient for TURP. This small amount is offset by the increased transfusion rate.

Hidden costs

There may be hidden costs associated with a change from TURP to TUVP. Prostate cancer is detected at a rate of ~15% in large series of TURP.[41] The lack of tissue for histological analysis in TUVP might lead to an increase in the use of preoperative transrectal ultrasound scanning in order to overcome this. This additional cost would reduce any possible economic advantage of TUVP.

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TABLE 23 *Additional procedures on trial patients*

	TURP	TUVP
Meatotomy	8	4
Otis urethrotomy	48	47
Urethral dilatation	10	13
TUIP	17	5
Optical urethrotomy	0	2
Litholapaxy	0	2
Bladder biopsy/transurethral resection of bladder tumour	1	2
Other	0	2

Protocol deviations

One patient in the TURP group underwent a different operation to the one to which he had been randomised. This patient had a TUVP and was one of two trial patients on the same operating list randomised the day before surgery. Unfortunately, this resulted in both of these patients receiving the incorrect operation.

A further five patients underwent transurethral incision of the prostate (TUIP) as their sole procedure. Six patients randomised to TUVP did not receive it. Five patients had TURP: four in error and one because of carcinoma of the prostate detected by on-table TRUS. The sixth patient did not undergo any operative intervention. These patients remained within their randomisation group for further analysis since this was performed on an ITT basis.

In addition to the primary procedure, a high proportion of patients underwent an additional procedure. Details of these additional procedures are given in *Table 23*.

At 2 years, data were available for 168 patients. Eighteen patients indicated that they wished to withdraw during the course of the study without giving a reason. Six patients were not written to because of an administrative error. Nine patients were known to have died during the course of the study and one was disabled by a cerebrovascular accident. Three were reported as ‘gone away’. Thirty patients failed to reply despite a reminder.

Chapter 4
Comments

Main findings

This study confirms that TURP and TUVP produce equivalent symptomatic relief in patients who are considered suitable for surgery for LUTS due to benign disease of the prostate. The two treatments also produce a similar improvement in the measure commonly used to provide objective measures of dysfunction in this condition. The symptomatic benefit appears to last at least 2 years after surgery. We conclude that the treatments are equally effective in this time frame.

The overall incidence of morbidity of these two electrosurgical modalities is similar. The principal difference is a marked reduction in the incidence of severe and prolonged bleeding after TUVP. The incidence of severe intraoperative bleeding was low and the fall in haemoglobin level postoperatively was significantly less. Bleeding sufficient to require blood transfusion was exceptional after TUVP and compared extremely favourably with the need for transfusion after TURP both in this study and others reported in the literature.

It has been assumed that the need to manage perioperative haemorrhage is the main determinant of postoperative hospital stay. It might therefore be expected that patients undergoing a procedure causing less bleeding (TUVP) would be discharged from hospital earlier than those who underwent a more bloody technique (TURP). In this study, the length of hospital stay was broadly equivalent in the two groups. This unexpected outcome requires explanation.

In this study, the direct NHS resource use was equally balanced between TUVP and TURP. The equipment used is similar between the two techniques, with a slight excess of cost relating to the electrodes used for TUVP. There is no significant difference between the time patients stay in theatre. The use of NHS resources after discharge is similar. The potential economy of significantly reducing the inpatient stay was not realised in this study.

Interpretation of the results

Our study was adequately powered to detect a clinically important difference in change of IPSS. We are confident that the study shows that both treatments produce an important improvement in symptoms and that no clinically important difference in effectiveness was demonstrated. We are also satisfied that the observed equivalence of effect on secondary objective outcome measures is genuine.

We were disappointed by the poor recruitment to our study from the relatively large potential pool of patients considered to be in need of surgery during the study period. This may be due in part to the understandable reluctance of patients to commit to a randomised study of invasive procedures. Age, ethnicity and economic factors may also be important. It is also possible that, for operational reasons, clinical staff at the contributing centres were deterred from entering patients because of the uncertainties and additional work involved in a clinical trial. Undoubtedly, the unusually severe service pressures prevalent during the study might have encouraged risk-minimising strategies. We are unable to ascertain whether the subset of patients who took part in our study was truly representative of the general population of patients requiring surgical treatment for bladder outflow obstruction. However, we do not consider that this invalidates our conclusion that the treatments are broadly equivalent in effect – a finding in accord with the results of other studies.

By contrast, we are not able to vouch for the incidence of less common adverse events as between the two techniques: much larger groups would be required to effect a reliable comparison. There was evidence that TUVP was associated with more urinary infection and less bleeding than TURP. Short-term and treatable adverse effects may be acceptable if one treatment has greater effectiveness or other advantages over an alternative. Longer term or irremediable consequences are likely to be less acceptable.

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Sustained impairment of sexual function after surgery was indistinguishable between the two groups. The onset of erectile failure in those who had enjoyed normal function was equally rare and retrograde ejaculation was equally common in both those who had had TURP and those who had had TUVP. The incidence of bladder neck and urethral stricture was too low in both groups to make any meaningful comparison.

Relatively rare but serious complications may have a profound effect on the acceptability of a surgical procedure. They may also impact significantly on the overall cost of the procedure if remedial treatment and litigation is expensive. For this reason, it is worth mentioning that one patient in each arm of the study suffered from postoperative incontinence, perhaps the most feared complication of transurethral prostatic surgery. Both patients had irritative symptoms preoperatively. The incontinence abated after 9 months of conservative management in the patient who had a TURP. The patient who suffered incontinence after TUVP remains wet and there is evidence that the urethral sphincter had been damaged in the procedure. Incontinence after TUVP has been reported previously but there is as yet no evidence that it occurs more frequently than after TURP and whether it is more common when the surgeon is new to the technique. Because there are theoretical reasons why TUVP may be more liable to cause sphincter damage through excessive local heating effects, this matter needs careful review.

It is extremely difficult to blind researchers effectively in studies of invasive procedures conducted by surgical teams who are also responsible for the aftercare of trial patients. In our pragmatic study, we aimed for a trial environment that reflected the day-to-day arrangements for urological care in the NHS. We could not exclude the possible operation of bias in decisions about bladder irrigation, catheter removal, the interpretation of adverse events and hospital discharge.

The research nurses responsible for collecting trial data were not involved in postoperative care. To administer the study, however, they needed to have access to the patient's clinical record. As a consequence, they were not blinded to the treatment administered. Full blinding of the research team would have required considerable more resource than was available for this study. Reassuringly, the primary outcome measure IPSS was determined by an instrument self-administered by the patient.

Inpatient hospital stay and transurethral surgery to the prostate

TUVP was associated with reduced perioperative bleeding and the need for blood transfusion was almost abolished. A surprising outcome of this study is that this did not lead to the expected reduction in the length of inpatient stay. This is at odds with most published accounts of TUVP.

One possible explanation for this is the possibility that the staff responsible for managing the patients on the wards treated them with the **expectation** that having undergone transurethral surgery to the prostate, the patients would stay in hospital for a length of time customary for TURP. This length of time is itself variable between institutions and may be reduced by the imposition of care protocols. Although those delivering aftercare were not formally blinded to the procedure performed, there was no particular reason for them to know the group to which the patient had been randomised.

Clearly, in a study that aims to deduce potential cost benefits related to reducing length of stay, it would introduce obvious bias if carers were briefed that one treatment was associated with a reduced need for inpatient care. In the original protocol, it was suggested that the time of discharge would be determined by a fixed protocol rooted in an objective assessment of blood loss postoperatively. The project Steering Group determined that such prescription was inappropriate to a pragmatic study of this kind. It was agreed that the outcome would be more likely to represent the likely outcome of introducing TUVP if staff were to manage patients according to existing norms.

The failure to observe a reduction in hospital stay was consistent across all the contributing centres – where a centre had a shorter length of stay, it was apparent in both groups.

This effect needs more careful study. It may well be that the duration and amount of bleeding are not the major determinant of length of stay in this group of elderly men undergoing endoscopic prostate surgery. Coexistent disease, poor social circumstances and non-availability of support at home may be important rate-limiting factors.

Our results show that TUVP is an effective treatment for men with symptomatic benign prostatic hypertrophy. The extent of the symptom relief, the improvement in flow rates and the ability to disobstruct the bladder are equivalent to TURP. The main advantage of TUVP over TURP is a reduction in bleeding, as evidenced by a lower

blood transfusion rate, smaller fall in haematocrit and a lower incidence of intraoperative heavy bleeding. These findings are in line with other published series.

Our main finding at odds with other studies is the failure to demonstrate an economically significant difference in the length of hospital stay between the two treatments. Hammadeh and colleagues,[22] working in the same health system, reported that patients who underwent TUVP stayed in hospital just under 1 day less than those who had TURP. If their findings could be replicated on a wider scale, there would be significant economic benefits for patients and the NHS.

There may be a number of reasons why our results do not mirror theirs. Multicentre studies tend to recruit a much more diverse patient population. The mean prostate size was larger than that reported by Hammadeh and colleagues. Perhaps most importantly, we included patients who were in acute retention of urine, on the grounds that these make up a significant proportion of those requiring prostatic surgery. It may also be the case that a higher level of expertise in a new technique can be found in single centres than can be achieved in routine practice.

The difference might also be explained by the exact variant of the TUVP electrode used in the study. We used the Circon-ACMI Fluted Vaportrode™ as opposed to the more commonly studied Circon-ACMI Grooved Rollerbar™. The fluted electrode was chosen because it was thought to remove more tissue through enhanced vaporisation effect. This may have been at the expense of less efficient coagulation.

This emphasises the difficulty in conducting meaningful large-scale studies of technologies that exist in multiple related variants. The choice of device, the variant of technique employed and variable familiarity with the procedure may produce uncontrolled and incalculable effects on the outcome of the study.

Our data on length of hospital stay were severely skewed and the median values of 4.0 and 3.0 days for TURP and TUVP may be a more valid representation than the mean values. This would certainly reflect the findings of most other studies of TUVP.

Management of NHS-funded RCTs

It proved more difficult to manage this trial than had been expected. The association with the NHS-funded PROTO was helpful in the planning stage of the project but the start date of our project had to be delayed until PROTO was staffed and running. Once the project had begun, the staff at PROTO were supportive and efficient in managing data sent to them. Dr T Peters gave extremely helpful statistical advice at a crucial stage of the project, with the result that the number of patients required for the study was reduced to a more manageable level. However, geographical separation meant that interactions were less frequent than might have been optimal.

In costing the proposal for this study, staff levels were minimised to keep the costs to a reasonable level. Unfortunately, the proposal underestimated the difficulty of maintaining the quality and completeness of data collection over a multicentre study of this kind. It was not possible within the resources available to institute a system of monitoring visits such as would be routine in any properly managed drug trial. In the event, the data were complete enough to ensure that the outcome was valid but there were unexplained gaps in the data and the follow-up rate at 2 years was disappointing. The CONSORT statement imposes challenging demands on those who run RCTs and it is unlikely that these demands can be met in full without a much higher and professional level of research governance than has been customary to date. Data monitoring to the level required is likely to be expensive if provided at a local level for each RCT. Considerations should be given to providing centralised oversight possibly based on a development of the PROTO model.

Recruitment to this study was severely compromised by resource difficulties suffered by the host providers during its course. Bed reductions and winter pressures meant that for a significant time during the study, hospitals were working on an 'emergencies only' or 'emergencies and cancer only' basis. This raised difficult ethical problems around whether patients who had been recruited to this study should have special priority in these circumstances. These were difficult or impossible to resolve at local level. Where patients recruited to the study were left for a prolonged period before randomisation, there was an increased risk that they would drop out of the study by getting their operation elsewhere or simply becoming disillusioned with the trial. If NHS-sponsored RCTs are to be conducted in NHS hospitals, there is a need for more central guidance in these matters.

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Christopher Fowler (Consultant Urological Surgeon and Professor of Surgical Education) was the principal writer, project lead and grantholder. William McAllister (Research Fellow) was the second writer and was responsible for the day-to-day management of the project. Roger Plail (Consultant Urologist) and Omer Karim (Consultant Urologist) were the centre leads for the project and commented on draft versions of the report. Qian Yang (Research Associate) carried out statistical analysis and was responsible for the statistical component of the report.

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