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Project title: Long-term outcome of men with lower urinary tract symptoms recruited to the CLasP randomised trial comparing transurethral resection of the prostate, conservative management and laser therapy

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Plain language summary

Lower urinary tract symptoms, such as increased frequency, hesitancy and a reduced stream, are common in older men and are usually related to enlargement of the prostate gland because of benign growth. Such symptoms lead to significant deterioration of quality of life. Traditionally, men with moderate or severe symptoms were treated by transurethral resection of the prostate (TURP). Today there is increased use of other treatment options including conservative management (often involving advice about lifestyle and bladder training), minimally invasive methods such as laser therapy, and drugs. The CLasP study, completed 15 years ago, is of high quality and compared standard surgery (TURP) with laser therapy and conservative management. The average follow-up in the CLasP study was 7.5 months, at which point TURP was the most effective, but had the most side-effects. Conservative management was the least effective but the safest. This current study provides long-term effectiveness of each of these treatments.

The GPs of all but 31 of the original 570 men were identified and contacted, approximately 50% of whom were deceased. After obtaining GP and patient consent medical notes were searched for 313 men – 55% of the original study men. Around 50% of those initially randomised to conservative management received surgery for their symptoms, many within a year of the original study, suggesting that for some it simply delays surgery. However, very few of these men went on to require any further surgery. Men who originally received TURP or laser therapy were three times more likely to require a second surgery for their symptoms. TURP and laser appeared as effective as each other in the long-term. The type of laser used in the original study has now been replaced in clinical practice; the effectiveness of newer versions is likely to be improved.

What is perhaps of most interest is that around 50% receiving conservative management received no surgery at all; the majority also receiving no drugs. Moreover, quality of life and symptoms were very similar amongst all the men after 15 years. Interviews with some of the men suggest that this may be partly due to the development of coping strategies.

Conservative management is an effective long-term treatment option for older men with troublesome lower urinary tract symptoms.

Keywords

LUTS (Lower Urinary Tract Symptoms), TURP (Transurethral Resection of the Prostate), Laser Therapy, Conservative management / watchful waiting, Retreatment, Quality of life.

Summary of research findings

Background

Lower urinary tract symptoms (LUTS) consistent with benign prostatic obstruction become increasingly common with age in men. In the UK over 50% of men over the age of 50 have some degree of LUTS and symptoms lead to impairment of quality of life. Standard surgical treatment has long been transurethral resection of the prostate (TURP), however, associated risks of morbidity have led to the development of minimally invasive treatments such as laser therapy, and the increased use of drugs and conservative management (CM).

Between 1994 and 1996, 570 men diagnosed with LUTS were recruited to one of three linked CLasP trials. Men were recruited from secondary care in Newcastle, Bristol and Sunderland. Trial A included 340 symptomatic men randomised to TURP, laser (non-contact neodymium (Nd): YAG laser) or CM. Trial B recruited 82 men with chronic retention and Trial C 148 men with acute retention. Those in Trials B and C were randomised to TURP or laser. All men were followed for an average of 7.5 months. Whilst observed to be less effective, laser and CM were shown to be acceptable alternatives to TURP in the short-term. However, long-term data were, and remain, lacking in this important clinical area. This current study provides long-term followup of between 13-15 years.

Aims and objectives

The primary aim of this research was to determine whether CM or laser carry increased or decreased risks of subsequent need for retreatment and clinical deterioration in the long-term compared with conventional TURP. Whilst the Nd: YAG laser is no longer used in the treatment of LUTS, current forms of laser are likely to be more effective and so long-term outcome is informative for future practice as well as of historic interest. A secondary aim is to ascertain differences in terms of cost-effectiveness.

Methods

The current status of men and Local Authority within which they were last registered with a GP was determined by the NHS Medical Research Information Services. Relevant GP practices were identified and contacted by Primary Care Support Agencies. For living, contactable men, study packs were forwarded via their GP with information detailing the study, a symptom and treatment questionnaire and a consent form for medical notes to be searched. For the deceased, GPs were requested to examine patient notes to ensure no known objection to being involved in research and provide consent for medical notes to be searched. Hospital notes were searched for details of treatment for LUTS since the original study (when not available GP notes were used where possible) and current medication for LUTS was extracted from GP notes.

The primary outcomes were the need for further treatment (surgical and non-surgical), time to definitive treatment (TURP) and quality of life. Secondary outcomes included current symptoms measured through the International Prostate Symptom Score (I-PSS). Analyses were performed for Trials A, B and C separately. However, small numbers of chronic and acute men followed up make these analyses exploratory only. All analyses were intention to treat and adjusted for age and centre.

Results

566 (99%) of the original men were traced, 4 having left the country. Of these, 274 were deceased and 292 living (mean age 80); a further 9 men died during the followup period. A flow diagram of the study is presented in Appendix I. Medical notes were retrieved for 286 men. Questionnaire data relating to treatment was available for a further 27 men, providing retreatment data for 313 men, 55% of the original 570. This proportion was consistent across Trials A, B and C and across treatment groups.

Surgical retreatment

Overall 19% of men received TURP and a further 7% an alternative surgery (laser, bladder neck incision, transurethral vaporisation of the bladder, transurethral needle ablation) after the initial CLasP study treatment.

There was strong evidence of a difference between the groups in terms of the need for surgical treatment during followup ($P < 0.0001$). As anticipated, those randomised to CM were more likely to receive surgical treatment than those originally randomised to either TURP ($OR = 7.9$, 95% CI 3.1 to 19.7) or laser ($OR = 9.3$, 95% CI 3.6 to 24.1) within Trial A. There was also evidence of a higher surgical retreatment rate amongst those randomised to laser compared to TURP amongst men in the acute trial only ($OR = 3.9$, 95% CI 1.2 to 12.2, $P = 0.022$). The same pattern was seen when only definitive treatment (TURP) was considered.

Given that men randomised to laser and TURP received a surgical treatment as part of the original study it is just as important to examine the total number of surgeries received by the different treatment arms. Whilst 53% of CM men received one surgical treatment during follow up only 6% received a second surgery. This is compared to 20% of lasers and 15% of TURP men who received surgery after initial study treatment. A logistic regression examining the odds of a second surgery provided no evidence of a difference between groups.

The median times to surgical intervention during followup were 2.9, 2.4 and 1.0 years for laser, TURP and CM respectively. The median time to a second surgical treatment for CM was 6.6 years. Cox Proportional Hazards models found strong evidence ($P < 0.0001$) that time to any surgery was shorter for CM compared to TURP ($HR = 6.1$, 95% CI 2.7 to 13.4) or laser ($HR = 9.6$, 3.9 to 23.4) in Trial A. No differences were found between TURP and laser for Trials A, B or C. The same pattern was seen when time to TURP only was considered. There was no evidence ($P = 0.43$) that time to second surgery was longer for CM men compared to TURP ($HR = 0.46$, 95% CI 0.13 to 1.55) or laser ($HR = 0.69$, 0.19 to 2.51) in Trial A, but this may be due to too few events.

Non-surgical treatment

At the point of followup or time of death, medication for LUTS was prescribed to 23% of CM men, 29% laser and 16% TURP. There was no evidence of a difference between treatment groups with the exception of an increased odds of medication amongst laser compared to TURP in the acute trial patients ($OR = 6.2$, 95% CI 1.5 to 25.4, $P = 0.011$).

Of those randomised to CM 53% (95% CI 41% to 66%) received a surgical treatment. 15% (6% to 23%) are known to have received non-surgical treatment only and for 32% (21% to 44%) there was no record of any treatment (although there may have been previous medication prescribed through general practice that we are not aware of).

Quality of life and symptom score

Mean scores were similar across the treatment groups for both I-PSS quality of life (laser=2.4, TURP=2.3, CM=2.2) and symptom scores (laser=11.7, TURP=10.2, CM=11.3) which were available for living men completing the questionnaire. For both measures a higher score corresponds to a worse outcome. Linear regression provided no evidence of any differences.

Economic evaluation

Health service resource use in terms of urological outpatient appointments and inpatient stays in relation to LUTS since the original study were abstracted from the medical records. A case note review was conducted on 286 patients. In the symptomatic group the mean number of outpatient appointments was greatest in the CM group (CM=5.3; laser=3.0; TURP=3.1). The CM group also had the greatest mean number of inpatient admissions for all surgical and non surgical categories (see Appendix II). For the 54 patients in the CM group there were 21 admissions for TURP, 8 for BNI, 4 for laser, 7 other surgical admissions and 8 non surgical admissions. In the chronic and acute patient groups, the mean number of outpatient appointments was greatest in the laser group (Chronic: 5.2 vs 4.2; Acute: 4.4 vs 2.4). Analysis is ongoing.

Qualitative interviews

A total of 21 interviews were conducted (9 Laser, 7 TURP, 5 CM). Interview transcripts were analysed thematically employing methods of constant comparison to compare emerging themes within and across transcripts (Not all interviews have yet been fully analysed). In general, participants were happy with the treatment they received for LUTS. Some had not expected to require additional treatment and were surprised when their symptoms reappeared, whilst others had been prepared for this possibility. Nocturia, frequency and poor flow were commonly reported, though most men described their symptoms as being milder than before active treatment. Whilst some men described the impact of their symptoms on quality of life in some detail (such as feeling exhausted due to nocturia) most felt their symptoms did not prevent their usual activities. On further probing, it appeared most learnt to live with their symptoms by developing coping strategies (such as well planned travel and reducing fluid intake) which in turn meant that further treatment was not always sought. Some also appeared to cope by attributing most of their symptoms, including erectile dysfunction, to their advancing age.

Conclusions

We were able to search the medical notes of 55% of the original CLasP men. This rate is largely due to the notes of many deceased being destroyed and lack of response from living men, which may in part be explained by age (indeed responders were on average 3 years younger than non-responders). There were few differences between laser and TURP with the exception of those in the original trial of acute patients where there was some evidence of the laser being inferior in terms of retreatment.

Whilst just over 50% of those randomised to CM received surgical treatment during follow up and for many these were within the first year, nearly 50% received no surgical treatment and up to 32% received no treatment at all. Very few CM men required a second surgical treatment. In addition, those randomised to CM reported similar quality of life and symptoms as those initially receiving surgery. Qualitative interviews suggest that this may at least partly be due to the development of coping mechanisms.

Patient and public involvement

Due to the nature and design of this study, in that it was a long-term followup of a previous trial, the potential for public/patient involvement was limited. We had however hoped that we would be able to identify one or two public/patient representatives to sit on the Steering Committee. Unfortunately this did not happen. We were keen for members of the original study to be identified as representatives but the initial process of tracing and contacting men was much more difficult and drawn out than anticipated so the potential to identify anyone was heavily delayed. In addition, the age of the men involved (average age 80) raised concerns about the potential additional burden that would be placed on them. In hindsight we wish we had pushed this further and identified someone perhaps from outside of the study and we would certainly do this in any future work.

We were lucky that consultations with the public/patient were conducted through qualitative interviews (with 21 men). These elicited views on the long-term treatment and management of lower urinary tract symptoms. These views will be incorporated into all presentations and publications resulting from this work and hence will help inform future practice.

Data sharing statement

See link

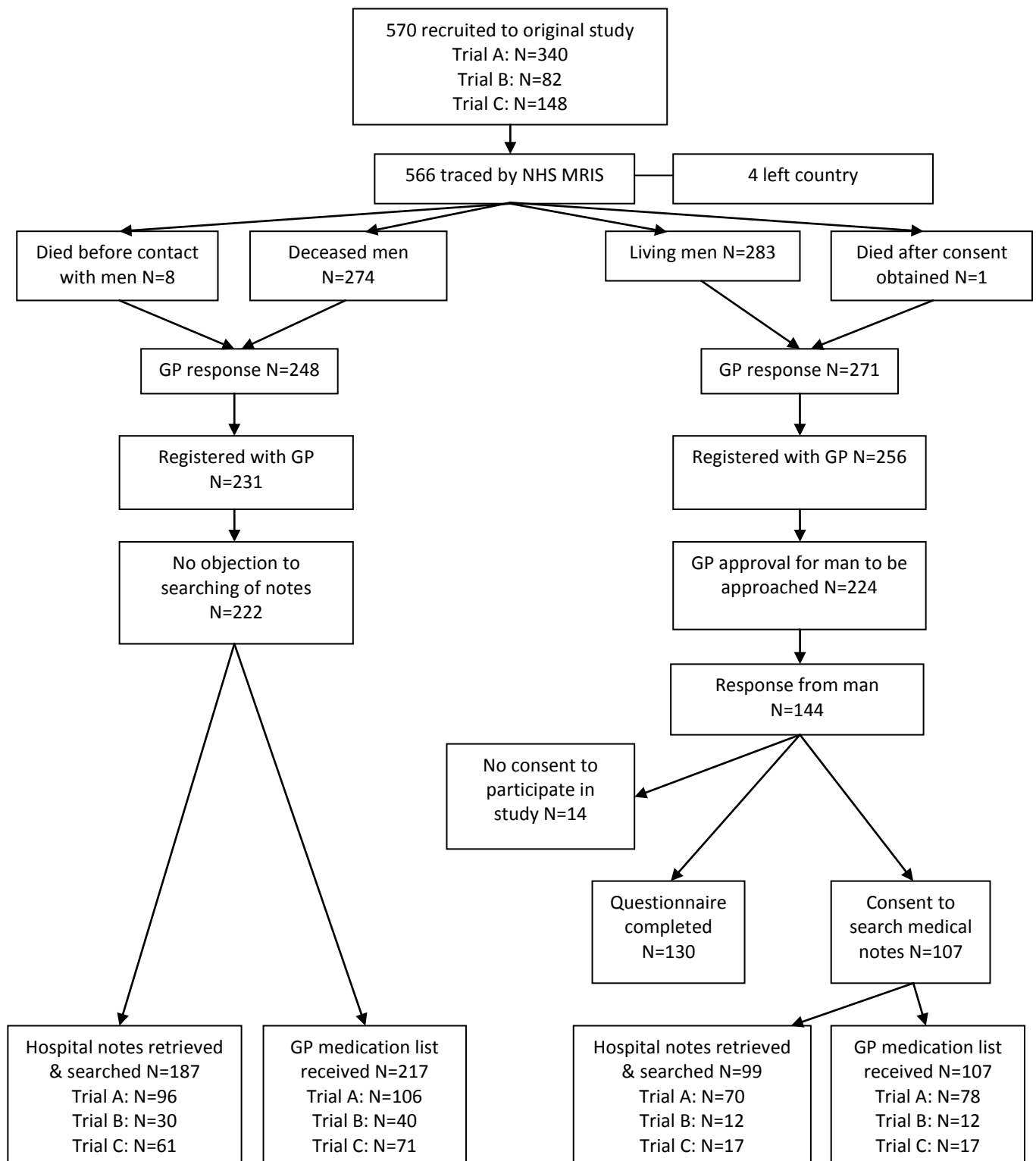
[\[https://www.nihr.ac.uk/documents/nihr-position-on-the-sharing-of-research-data/12253\]](https://www.nihr.ac.uk/documents/nihr-position-on-the-sharing-of-research-data/12253) for the NIHR position of the sharing of research data. The NIHR strongly supports the sharing of data in the most appropriate way, to help deliver research that maximises benefits to patients and the wider public, the health and care system and which contributes to economic growth in the UK. All requests for data should be directed to the award holder and managed by the award holder.

Disclaimer

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This project was carried out between December 2009 and April 2012. This final report has not been peer-reviewed. The report was examined by the Programme Director at the time of submission to assess completeness against the stated aims.

Flow diagram for the CLasP long-term followup



Trial A: Symptomatic patients; Trial B: Chronic retention men; Trial C: Acute retention men

Appendix II: Economic evaluation

The Mean (st.dev) of resources used by the different patient groups by their randomisation allocation						
Resource item	N	Laser Therapy	N	TURP	N	Conservative management
		Mean (st.dev)		Mean (st.dev)		Mean (st.dev)
Number of outpatient appointments						
Symptomatic	59	3.0(4.40)	53	3.13 (4.30)	54	5.28 (5.74)
Chronic	17	5.24(6.42)	25	4.16(6.43)		
Acute	39	4.38 (5.01)	39	2.38 (3.07)		
Number of admissions for TURP						
Symptomatic	59	0.05 (0.29)	53	0.11(0.32)	54	0.39(0.49)
Chronic	17	0.24 (0.44)	25	0.12 (0.33)		
Acute	39	0.38 (0.54)	39	0.13 (0.34)		
Number of admissions for BNI						
Symptomatic	59	0.07 (0.25)	53	0.02 (0.14)	54	0.15 (0.36)
Chronic	17	0 (0)	25	0.08 (0.28)		
Acute	39	0(0)	39	0.03 (0.16)		
Number of admissions for laser therapy						
Symptomatic	59	0.02(0.13)	53	0.02(0.14)	54	0.07 (0.26)
Chronic	17	0(0)	25	0(0)		
Acute	39	0.03 (0.16)	39	0 (0)		
Number of other surgical admissions						
Symptomatic	59	0.1 (0.4)	53	0.09 (0.4)	54	0.13 (0.34)
Chronic	17	0.06 (0.24)	25	0.08 (0.28)		
Acute	39	0.03 (0.16)	39	0.05 (0.22)		
Number of other non surgical admissions						
Symptomatic	59	0.1 (0.36)	53	0.11 (0.42)	54	0.15 (0.53)
Chronic	17	0.06 (0.24)	25	0.08 (0.28)		
Acute	39	0.33 (0.66)	39	0.36 (1.5)		