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Diagnostic assessment of lower urinary tract symptoms in men considering prostate surgery; a non-inferiority randomised controlled trial of urodynamics in 26 hospitals.

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Objective

Prostate surgery can improve lower urinary tract symptoms (LUTS) by relieving bladder outlet obstruction (BOO). However, surgery is less effective without BOO, or if detrusor underactivity (DU) is present. Urodynamics (UDS) can identify BOO and measure detrusor activity, but evidence in clinical practice is lacking. UPSTREAM (Urodynamics for Prostate Surgery Trial: Randomised Evaluation of Assessment Methods) evaluated whether a care pathway including UDS would reduce surgery without increasing urinary symptoms.

Design, setting and participants

UPSTREAM is a pragmatic, non-inferiority randomised controlled trial in 26 hospitals in England (ISRCTN56164274) in men with bothersome LUTS where surgery was an option.

Intervention

Participants were randomised (1:1) to routine care (RC) diagnostic tests, or routine care plus urodynamics (UDS).

Outcome measures

The primary outcome was International Prostate Symptom Score (IPSS; patient reported outcome scale from 0 to 35 points) 18-months post-randomisation, with a non-inferiority margin of one point. Urological surgery rates were a key secondary outcome.

Statistical analysis

The primary outcome was compared between the arms using linear regression, analysed on an intention-to-treat basis.

Results and limitations

Between October 2014 and December 2016, 820 men (median age 68 years) were randomised (393 and 427 in RC and UDS arms, respectively). The UDS arm showed non-inferiority of mean IPSS scores (UDS 12·6; RC 13.1; adjusted difference at 18 months -0·33 (95% CI -1·47, +0·80)). In the UDS arm, 153/408 (38%) received surgery compared with 138/384 (36%) for RC (adjusted OR 1·05; 95% CI 0·77, 1·43). 428 adverse events (UDS 234; RC 194) were recorded, with related events similar in both arms, and 11 unrelated deaths.

Conclusion

In this population, the UDS randomised group was non-inferior to RC for IPSS but did not reduce surgical rates. The study shows that routine use of UDS in evaluation of uncomplicated LUTS has a limited role and should be used selectively.

Patient summary

For men with uncomplicated lower urinary tract symptoms, the symptom improvements after treatment and the number of operations done are similar, whether or not urodynamic tests are done in addition to routine tests. Accordingly, routine use of UDS has a limited role in this population group.

Introduction

Lower urinary tract symptoms (LUTS) are associated with substantial personal and societal costs, and detrimental impact on quality of life (QoL) [1-4]. Potential mechanisms contributing to LUTS include benign prostate obstruction (BPO) and weakened bladder muscle (detrusor underactivity; DU), which both give similar voiding symptoms [5]. In addition, overactive bladder (OAB) [6,7] and nocturnal polyuria may cause storage LUTS [8]. Guidelines indicate to offer interventional treatment, e.g. TURP, if LUTS are severe and unresponsive to conservative treatment [9,10]. Symptom scores, bladder diary, physical examination, urinalysis and uroflowmetry (maximum flow rate (Q_{max}) and post void residual (PVR)) are routinely used for LUTS assessment [9,11]. However, none of these tests can distinguish BPO from DU. Since only LUTS due to BPO is reliably expected to improve with surgery [12], the routine assessments leave uncertainty for recommending therapy.

Urodynamics (UDS) uses pressure flow studies (PFS) to distinguish BPO from DU, by associating a slow Q_{max} with either high detrusor pressure or low detrusor pressure respectively [13]. High pressure generating slow flow is diagnostic for BPO, as quantified by the BOO Index (BOOI). DU severity can be quantified using the Bladder Contractility Index (BCI) [14]. UDS also includes filling cystometry to assess storage function, which can identify detrusor overactivity (DO). However, due to lack of evidence [9,11,15,16], guidelines do not routinely include UDS. Using UDS could avoid "unnecessary" surgery in men whose voiding LUTS is actually caused by DU. However, UDS also has costs and involves catheterisation, potentially without changing the management recommendation. Thus, there is considerable regional variation in use of UDS (from 0.2 to 5.0 tests annually per 1000 population) [17]. Gaining meaningful evidence to improve male LUTS assessment is an identified priority [9,11].

UPSTREAM (Urodynamics for Prostate Surgery Trial: Randomised Evaluation of Assessment Methods) is a randomised controlled trial (RCT) of men with bothersome LUTS referred to urology departments in 26 UK hospitals, where surgery was being considered [18]. All men had received conservative and/ or medical therapy, and had sufficiently bothersome LUTS to enter the secondary care diagnostic pathway to consider whether surgical intervention was indicated. UPSTREAM was powered to ascertain non-inferiority in symptom severity (International Prostate Symptom Score (IPSS)) at 18-months post-randomisation. The key secondary outcome was surgery rates.

Methods

Study design and participants

The trial protocol and statistical analysis plan (SAP) are published elsewhere [18,19]. To summarise, UPSTREAM is a pragmatic, two-arm, multicentre, non-inferiority RCT to determine the clinical and cost-effectiveness of UDS for diagnosis and management of BOO in men (≥18-years) with bothersome LUTS, where surgery was potentially being considered. Exclusion criteria were; catheter use for bladder emptying, relevant neurological disease, current treatment for prostate or bladder cancer, previous prostate surgery, unfit for surgery, and/or unwilling to comply with trial requirements. Baseline characteristics and initial diagnostic testing outcomes are reported separately [20]. UPSTREAM was approved by the NHS Research Ethics Service (South Central – Oxford B, reference 14/SC/0237). The study was overseen by an independent Data Monitoring Committee and Trial Steering Committee. The trial was registered with the International Standard Randomised Controlled Trial Number (ISRCTN) registry on 8 April 2014 (ISRCTN56164274) and sponsored by North Bristol NHS Trust (NBT; reference number 3250).

Procedures

Men were randomised to undergo either routine non-invasive tests set out in the applicable NICE Guideline [9] (Routine Care arm; control), or the routine tests supplemented by UDS (UDS arm; intervention). Given the pragmatic design, research centres could conduct additional 'discretionary' tests (e.g. PSA testing, cystoscopy, prostate volume measurement) [20]. Once men had undergone assessments, a treatment recommendation was made by the surgeon, and the patient decided whether to accept the treatment recommendation. No specific management pathway requirements were imposed by the trial. The primary outcome was captured at 18-months post-randomisation.

Randomisation and masking

Simple randomisation, without stratification or minimisation techniques, was employed via a telephone/web-based system hosted by Bristol Randomised Trials Collaboration (BRTC). 'Centre' was adjusted for in all analyses. Given the nature of UDS, men and hospital staff

were not blinded to randomised allocation. The research team (co-applicants) were blinded to study arm throughout recruitment and analyses, however, the junior trial statistician was unblinded to allow reporting to the Data Monitoring Committee.

Outcomes

Data were collected between October 2014 and August 2018, with details of outcome measures published elsewhere [18-20]. In brief, the primary outcome was the difference in IPSS between the two arms at 18-months post-randomisation [21,22], with a non-inferiority margin of one-point. Scores could range from 0-35, with higher scores reflecting more severe symptoms. The IPSS was incorporated into a patient-completed questionnaire booklet, provided at 0- (baseline), 6-, 12-, and 18-months, collected via paper copy, online, or telephone call with trained central team staff. The key secondary outcome was surgery rates (proportion of men in each study arm having surgery) within 18-months of randomisation. Surgical data were obtained via case report forms (CRFs) completed by trained hospital staff from medical record review.

An additional secondary outcome was the relative harms of UDS, and subsequent treatment, as measured by adverse events (AEs); see the protocol paper for definitions [18]. Events related to surgical treatment were classified by sites using the Clavien-Dindo classification [22], reviewed by an independent clinician. Other patient reported outcome measures (PROMs), namely the International Consultation on Incontinence Questionnaire for MLUTS (ICIQ-MLUTS) and associated sexual matters (ICIQ-MLUTSsex) were included within the questionnaire booklets. IPSS-QoL was also measured (scored 0-6, with higher scores reflecting worse QoL). ICIQ three-day bladder diary were completed at baseline and 18-months, and men who had UDS were asked to complete the ICIQ-UDS-Satisfaction questionnaire.

Clinical outcomes (including DRE, uroflowmetry (Q_{max}, VV and PVR), UDS and additional tests) were also obtained via CRFs completed by hospital staff from medical records. Additional uroflowmetry data were collected for men who underwent surgery, approximately 4-months after surgery (+/- 1-month). The method (quality) of UDS testing is reported elsewhere [18]. An internal validation of surgery recommendations was carried out after the trial (*post-hoc*), by the trial office, whereby data on uroflowmetry and urodynamics were reviewed for each patient to assess whether or not surgery should have been recommended.

Statistical analysis

Statistical analyses were conducted as per the published SAP [19], using STATA software, version 15.1 [23]. All primary and secondary comparative analyses adopted the intention-to-treat principal, with no imputation for missing data, adjusting for centre and the relevant baseline measure. To avoid perfect prediction, binary PROMS were not adjusted by centre. All analyses, comparing arms, used Routine Care as the reference group so that findings could be interpreted as the effect of including UDS in the patient pathway.

The primary analysis, IPSS score at 18-months, was compared between the arms using linear regression, adjusting for centre and baseline IPSS score. The sample size required to test for non-inferiority was set at 800 men, to allow for a non-inferiority margin of one-point, standard deviation of five-points, attrition of 20% and power of 80%. Non-inferiority was to be declared if the upper limit of the two-sided 95% CI, comparing UDS to Routine Care, was less than one-point. More details on the sample size calculation and non-inferiority margin can be found in the published SAP [19].

As sensitivity analyses, a *per protocol* and complier average causal effect model (CACE) were carried out to ensure the intention-to-treat model results were robust. The *per protocol* analysis restricted the primary comparison to only include those who received their assigned treatment. The CACE analysis utilised the same patients as the primary analysis but used allocation in an instrumental variable analysis. Further details on the additional sensitivity analyses carried out can be found in the supplementary appendix.

All sub-group analyses for the primary outcome were prespecified in the published SAP [19]. To assess the effect of storage dysfunction, a binary variable separated nocturia more than once per night from nought to once. IPSS questions 2 (frequency), 4 (urgency) and 7 (nocturia) were combined and the median was used to split the sample into high/low storage dysfunction severity groups. An additional *post-hoc* analysis examined interaction between treatment allocation and surgery on change in IPSS score, to explore whether surgery was more effective in one of the treatment groups. Change in IPSS score was used, instead of adjusting for baseline IPSS, to avoid the selection bias caused by the differing baseline characteristics of those who did and did not receive surgery. A likelihood ratio test was then

used to compare linear regression models with and without an interaction between treatment arm and surgery.

AEs were explored at the event level and patient level on an 'intention-to-treat' and 'as-treated' basis.

Results

Between 01 October 2014 and 31 December 2016, 8671 men were screened (see [20]) and 820 were recruited (Figure 1); median age was 68 years and 67% had comorbidities. Baseline characteristics were similar between the study arms (Table 1), as detailed elsewhere [20]. Of the 427 men randomised to the UDS arm, 353 (83%) had UDS during the 18-months of follow up. Of the 393 men randomised to Routine Care, 28 (7%) received UDS. There were 67 withdrawals, 39 (9%) and 28 (7%) for the UDS and Routine Care arms respectively; the most common reason was poor health. After adjustment for baseline IPSS, the analysable sample at 18-months was 641 (78%); 328 (77%) and 313 (80%) for the UDS and Routine Care arms, respectively, with similar loss to follow up of the primary outcome (Figure 1).

Primary outcome of IPSS

The UDS arm demonstrated non-inferiority for patient reported LUTS, compared with Routine Care at 18-months, with a difference in mean IPSS of -0·33 (95% CI -1·47, 0·80); below the 1.00 non-inferiority margin (Table 2). The CACE analyses of IPSS results were generally similar to the ITT results. The upper confidence interval in the *per protocol* analysis was 1.05, slightly above the non-inferiority margin (Table 2). The patients in the Routine Care arm who received urodynamics (n=24) had higher IPSS scores at 18-months than compliers (n=305) in the routine care arm (17.3 vs 12.8), although this is a small sample size to base this on and the difference was also evident at baseline (22.6 vs. 19.2).

Other sensitivity analyses were also generally in agreement with the ITT analyses (Supplementary Table 1) and further details can be found in the supplementary appendix.

Pre-specified tests of interaction explored potential effect modifiers. Although underpowered, there were no evident interactions between subgroups, such as age or urinary function, on the effect of study arm on IPSS (Supplementary Table 2).

Secondary clinical outcomes

The hypothesised reduction in surgery rates in the UDS arm was not shown at 18-months. 38% of men (153/408) in the UDS arm received surgery during the 18-month period, compared with 36% (138/384) in the Routine Care arm, OR 1.05 (95% CI 0.77, 1.43) (Table 3). Likewise, the proportions of men offered surgery were 49% (196/397) *versus* 48% (182/378) respectively, (OR 1·02; 95% CI 0·76, 1·38). The *post-hoc* internal validation of surgery recommendations also gave figures that suggested equal proportions in the two arms, with 65% of men being recommended in both 'as treated' arms (Supplementary Table 3). Median time between randomisation and surgery was 216 days in the UDS arm (IQR 141-327 days) compared with 177 days in the Routine Care arm (IQR 106-284 days). In both groups at least 75% of men had TURP, and the remainder underwent a laser procedure, bladder neck incision, Urolift or another procedure.

In all men reporting IPSS, mean scores decreased from 18·5 (n=403) at baseline to 12·6 (n=340) at 18-months in the UDS arm and from 19·4 (n=371) to 13·1 (n=329) in the Routine Care arm (Tables 1 and 2). In an exploratory *post-hoc* analysis, there was some evidence to suggest that UDS was an effect modifier of surgery, with surgery being potentially more beneficial in the Routine Care arm, $p<0.001$ (Figure 2, Supplementary Table 4).

Secondary patient-reported outcomes

The mean difference for the IPSS QoL score was -0·07 (95% CI -0·32, 0·18), slightly lower in the UDS group, with an interval that excludes the minimal clinically important difference (MCID) of 0·5 (Table 4). Mean IPSS QoL scores dropped from an average of 4.1 to 2.7 in the UDS arm and 4.2 to 2.7 in the Routine care arm. Other urinary outcomes were similar, with general improvement across all symptoms by 18-months (Supplementary Table 5). There was some evidence to suggest nocturia (more than once per night) improved more in the UDS arm, although this may have been a chance finding, given the number of comparisons of secondary outcomes. Sexual patient reported outcomes were similar, and the proportion of patients experiencing sexual symptoms at 18-months were similar to the levels seen at baseline (Supplementary Table 5). There was no evidence to suggest a difference between the study arms for flow rate (Q_{max}) (Table 3).

Adverse events

In total, there were 428 AEs in the UPSTREAM study, 234 in the UDS arm and 194 in the Routine Care arm. There was no evidence to suggest that one study arm was superior to the other for AEs per individual (Supplementary Table 6a). At the event level, the number of related SAEs was similar across the two arms (Supplementary Table 6b). There were slightly more events overall in the UDS arm, largely due to the events that were deemed related to UDS (for example, urinary tract infection). There were 11 deaths during the 18-months of follow up, 9 of which were in the UDS arm; all were deemed unrelated to diagnostic testing or treatment.

Discussion

The primary outcome showed that a pathway of routine care including UDS, and the subsequent treatment, was non-inferior to Routine Care in terms of symptomatic urinary outcome. This was a population of men who had bothersome LUTS despite first line therapy, and were being considered for surgical treatment. We hypothesised that by identifying DU, UDS would reduce surgery rates, but such a reduction was not identified. UPSTREAM provides robust, high-level clinical evidence regarding use of UDS for male LUTS, which is something that literature reviews had identified as missing [9,15,24]. In our systematic review [15], we found evidence from one single-centre trial suggesting that UDS changed the management of LUTS and that men receiving clinical assessment alone were more likely to undergo surgery. No difference was noted between groups in the IPSS before and after intervention, so we concluded that evidence regarding the value of UDS was insufficient. Likewise, the UK NICE Clinical Guideline on LUTS in men: management (CG97) indicated that future research should clarify whether UDS could improve outcome of surgery, by identifying which patients had BOO. The UPSTREAM study responds to that call, and supports a position that properly-applied Routine Care testing provides sufficient assessment of LUTS when considering surgery in men comparable to the trial population.

UDS evidently remains important in some male LUTS settings. The qualitative evaluation we undertook identified a key reason for men wanting to undergo urodynamics was perceiving value in providing additional insight to them and their clinicians [25], not merely ‘sufficient’

information. Furthermore, some men experienced deterioration in symptoms despite surgery, and we plan to identify any predisposing characteristics in upcoming analyses. The study excluded men if they had a relevant neurological disease, or had previously undergone prostate surgery. In these groups there may be a higher prevalence of DU [12,26], indicating that UDS has a role.

The non-inferiority design was chosen since it was hypothesised that surgery rates would be lower in the UDS arm, due to the ability to exclude LUTS due to DU. In these cases, surgery might not be effective or could make the man's overall health worse (for example, due to complications such as incontinence). However, the key secondary outcome measure of surgery rates also showed no difference in the UDS and Routine Care arms, at 38% and 36% respectively. To explore this further, the rates at which surgeons recommended surgery were captured. In addition, an internal exercise was undertaken matching source data to a checklist of parameters for considering surgery (Supplementary table 3). These likewise found no difference between arms in potential surgery recommendation. In order to evaluate crossover between arms, a CACE analysis was undertaken to allow unbiased assessment of treatment effect, after separating the intervention arm into compliers and non-compliers. The CACE analyses of IPSS results were generally similar to the ITT results. Thus, the lack of difference between arms is not resulting from issues of crossover or decision-making, and can be supported objectively.

On inspection of the interaction between surgery and treatment allocation, there was evidence to suggest that surgery in the Routine Care arm led to larger drops in IPSS score. This may be due to delayed surgery in the Urodynamics arm, hampering the long-term benefits of surgery, or perhaps it indicates that other diagnostic tests may be better at identifying patients where surgery may be beneficial. Long term follow up could provide the answer. Quality of testing clearly could influence the conclusions, so we undertook a quality control exercise which we reported previously [27]. In brief, we found several errors of standardisation, testing, interpretation and equipment maintenance. Generally these had a relatively low risk of adverse implications for decision making. However, erroneous diagnosis of BOO was identified in 5.5% of tests, which is a serious error of interpretation, due to the risk of undergoing "unnecessary" surgery.

The overall rates of surgery were lower than anticipated when the study was designed. The design used surgery rates derived from audit of local practice, and publications of surgical

trials. Nonetheless, trends in lower likelihood for surgeons to recommend surgery, and for patients to accept surgery, progressed during the timescale of the study [28,29]. There was no evident signal of any difference in surgery rates to suggest an underpowered study. Thus, whilst there was a lower rate of surgery than planned for, it does not affect this study's conclusion.

The high number of men screened to identify the study population was determined by the clinical setting from which identified potential recruits were identified. Where sites screened in general urology clinics, in which eligible LUTS cases were a minority, a large number of patients was screened. This does not impact on the study interpretation, as the patient population is clearly defined by the eligibility criteria.

We identified there was variability in the therapeutic pathway across the 26 hospitals. For example, several patients had not fully completed their LUTS treatment at 18 months, or had completed it relatively recently. Clinically, a 12-month timeframe after surgery is appropriate to establish response. Thus, a longer-term follow up of participants could provide complete surgery rates in both arms, and symptomatic outcomes. The AEs occurred in rates similar to those seen in other surgical randomised trials [30]. There was a slight predominance in the UDS arm, consistent with the known rates of complications for UDS testing. There were 11 deaths, but these did not result from study-related procedures or interventions, as confirmed by an independent reviewer.

While adherence to the study arms was reasonable, there was a slightly higher likelihood of men crossing over from the UDS arm to the Routine Care arm. This may suggest some unwillingness to contemplate an examination which involves catheterisation. However, for those men who actually underwent UDS, the overall satisfaction rates with testing were very high, as we reported previously [20,25]. The additional time of contact with healthcare professionals might explain the high satisfaction levels; qualitative research identified the value of clear and personalised interpretation of symptoms in helping the man come to terms with his LUTS and decide on treatment, regardless of treatment [25]. Research centres were permitted to conduct additional 'discretionary' tests (e.g. PSA testing, cystoscopy), as these were not considered influential on relative indications for urodynamic testing.

Going forward, we believe that future research should focus on individual predictive factors influencing outcome of surgery. We observed that some patients did not have a good symptomatic outcome from surgery, and further analyses are being undertaken to establish

whether any diagnostic feature anticipated bad outcome with surgery; establishing features to anticipate detrimental effect of surgery is a priority. Research should also extend the range of potential participants to cover co-morbidities, including people with a background of neurological impairments. We also anticipate publishing the health economic findings in due course.

In identifying that the UDS pathway was non-inferior to Routine Care for symptom outcomes, but without a concomitant reduction in surgery rates, the UPSTREAM trial establishes that Routine Care provides sufficient testing for assessing LUTS when considering surgery in men comparable to the trial population. Urology departments can now move towards an evidence-based reduction of UDS. This must be in the context of reliable capture and interpretation of the Routine Care evaluations (history and examination, symptom score, bladder diary, urinalysis, uroflowmetry) [27]. Notably, there remains a clear expression by individual patients that they are keen to have access to maximum information to advise their decision-making [25]. Thus, delivery of UDS is not supported as a service-level approach to reducing surgery rates, but is desirable for an individualised approach responsive to supporting decision-making.

Conclusions

Including UDS in the diagnostic tests for male LUTS resulted in a non-inferior symptom outcome (IPSS) to routine care, 18-months post-randomisation. It did not, however, influence rates of surgery for treating BOO. Results of this study do not support routine use of UDS for men with suspected BOO. However, the large number of men who saw modest symptom change, or evident deterioration, suggests the need to interrogate the diagnostic pathway further, particularly for predictive features to identify men at risk of poor outcome.

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Data sharing

The study protocol and statistical analysis plan are available via publications cited in the text. Reasonable data sharing requests, including a methodologically sound proposal, should be made to the corresponding author. Requests will be reviewed with advisement of the Trial Management Group (TMG) and study Sponsor (North Bristol NHS Trust). This statement may be revised at a later date by the TMG.