BPH: Disease State, Outcome Measures, and Treatment Efficacy

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Scope of Discussion

• Briefly discuss the causes of BPH/bladder outlet obstruction
• Thorough discussion of disease process and symptoms
• Review of medical treatment options and efficacy of medical treatment
• Review of surgical treatment options and efficacy of surgical treatment
Pathologic BPH

Prostatic Zones

• The prostate consists of three distinct zones.
• Obstruction is caused by growth of the blue transition zone shown here.
• This zone can become very large.
Definitions

- **BPH**: Benign Prostatic Hyperplasia
- **LUTS**: Lower Urinary Tract Symptoms
- **BOO**: Bladder Outlet Obstruction
BPH/LUTS: What do we measure?

- Symptom Severity
- Urinary Flow (Qmax)
- Post Void Urine Residual
- Prostate Size
- Voiding Pressure (Urodymanics)
- Cystoscopic Findings
American Urological Association Symptom Index

- Developed and validated by the multidisciplinary measurement committee of the AUA
- 210 BPH patients and 108 controls
- Internally consistent (Cronbach’s $\geq$0.86)
- Excellent test-retest reliability ($r=0.92$)
- Selection of BPH Vs. controls (0.85)
- Response to TURP (17.6 to 7.1)

How Sensitive is the AUA Symptom Score (IPSS) ?

• We agree that the AUA Symptom Score is useful, but how big of a change needs to occur before the patient perceives an improvement or worsening of their symptoms ?
<table>
<thead>
<tr>
<th>Assessment of Change</th>
<th>No. Pts.</th>
<th>$\Delta$ Symptom Score</th>
<th>Percent Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marked</td>
<td>223</td>
<td>$- 8.8 \pm 0.34$</td>
<td>- 57</td>
</tr>
<tr>
<td>Moderate</td>
<td>298</td>
<td>$- 5.1 \pm 0.29$</td>
<td>- 32</td>
</tr>
<tr>
<td>Slight</td>
<td>347</td>
<td>$- 3.0 \pm 0.27$</td>
<td>- 16</td>
</tr>
<tr>
<td>None</td>
<td>253</td>
<td>$- 0.7 \pm 0.31$</td>
<td>- 2</td>
</tr>
<tr>
<td>Worse</td>
<td>24</td>
<td>$+2.7 \pm 0.93$</td>
<td>+ 19</td>
</tr>
</tbody>
</table>

AUA Symptom Score

- Maximum Score = 35
- Mild Sx. 0-7
- Moderate Sx. 8-18
- Severe Sx. 19+
Symptom Score vs. Age

Implications of the AUA Symptom Score

• Patients with mild symptoms (<8) should not be offered either medical or surgical treatment
• Those with moderate symptoms should be offered medical therapy as initial treatment
• Either medical or surgical treatment is appropriate initial treatment for severely symptomatic individuals (AUA SS >19)
Uroflowmetry

- Flow rate measurements are inaccurate if the voided volume is less than 125-150 ml
- Single best noninvasive urodynamic test, but a cut-off value cannot be determined
- Peak urinary flow rate (Qmax) is more specific for BPH than average uroflow
- Qmax < 15 ml/sec does not differentiate between obstruction and bladder failure
Urinary Flow Rate

- A person without bladder outlet obstruction produces voiding curve as shown here (Qmax = 23 ml/sec)
- Obstruction causes a marked flattening of the curve
Peak Uroflow Vs. Age


n = 2113
Postvoid Residual Urine (PVR)

• PVR has significant individual variability that limits its clinical usefulness
• PVR does not correlate well with other signs and symptoms of prostatism
• Large clinical trials have demonstrated higher rates of BPH progression in patients with progressively increased PVR
Effect of Prostate Size

• AUA SS administered to 2115 men
• Glands > 40cc were 3 times (1.6-5.1) more likely to have moderate or severe symptoms
• Glands > 40cc were 2.3 times (1.3-4.1) more likely to be bothered by their symptoms
• Less useful on an individual basis

Pressure-Flow Studies

• Pressure-flow urodynamic testing is indicated if the patient has moderate or severe symptoms inconsistent with other parts of the work-up, if they have failed prior invasive treatment, or if overt neurologic disease is present.

• Differentiates between prostatic obstruction and bladder decompensation or overactivity.
Pressure-Flow Testing

- Measure bladder pressure and urinary flow rate simultaneously
- $Q_{max} < 15 \text{ cmH}_2\text{O}$ and $P_{det} > 45 \text{ cmH}_2\text{O}$
- Most studies unequivocal
BPH Treatment Today:
Differing efficacy and side effects of various treatments make a careful pre-op evaluation important

- Watchful Waiting
- Medical Therapy
- “Less Invasive” Treatments
  - Microwave Thermotherapy and TUNA
- Operative Therapy
  - TUIP, Laser Prostatectomy, TURP, Open Prostatectomy
BPH: MTOPS DATA

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MTOPS
Primary Research Question

• To Determine if Medical Therapy Prevents or Delays the Clinical Progression of BPH as defined by one of the following:
  • Acute urinary retention (AUR)
  • Renal insufficiency due to BPH (> 50% rise in baseline serum creatinine & > 1.5 mg/dl)
  • Recurrent UTI or urosepsis
  • Incontinence (socially unacceptable)
  • ≥ 4 - Point Rise in Baseline AUA Symptom Score confirmed within 2 - 4 weeks
Evidence for Combination Therapy?

- Until MTOPS combination therapy trials were of short duration or lacked placebo controls
- Two randomized, controlled, 12-month studies\(^1,2\)
  - **VA COOP Study**: placebo-controlled, multicenter study in 1229 men with BPH in US VA System
    - Placebo vs finasteride vs terazosin vs combination
  - **PREDICT Study**: placebo-controlled, multicenter study in 1095 men with BPH in Europe
    - Placebo vs finasteride vs doxazosin vs combination

VA COOP and PREDICT Trials
Change in AUA Symptom Score at 1 Year

VACOOP: Lepor H et al. NEJM. 1996;335:533-539; PREDICT: Kirby et al, Urology 2004
VA COOP and PREDICT Trials
Change in Peak Flow Rate at 1 Year

Recruitment & Randomization

Randomized = 3,047

Screening Visit 1 = 4,391
Screening Visit 2 = 3,483

Placebo = 737
- Placebo Doxazosin
- Placebo Finasteride

Finasteride = 768
- Placebo Doxazosin
- Active Finasteride

Doxazosin = 756
- Active Doxazosin
- Placebo Finasteride

Combination = 786
- Active Doxazosin
- Active Finasteride

Dose: 5mg Finasteride; 4 or 8 mg Doxazosin
## BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Doxazosin</th>
<th>Finasteride</th>
<th>Comb</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>737</td>
<td>756</td>
<td>768</td>
<td>786</td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td>62.5 ± 7.5</td>
<td>62.7 ± 7.2</td>
<td>62.6 ± 7.3</td>
<td>62.7 ± 7.1</td>
</tr>
<tr>
<td><strong>Race (% White)</strong></td>
<td>82</td>
<td>83</td>
<td>84</td>
<td>81</td>
</tr>
<tr>
<td><strong>AUA Score</strong></td>
<td>16.8 ± 5.9</td>
<td>17.0 ± 5.8</td>
<td>17.6 ± 5.9</td>
<td>16.8 ± 5.8</td>
</tr>
<tr>
<td><strong>TRUS (ml)</strong></td>
<td>35.2 ± 18.8</td>
<td>36.9 ± 21.6</td>
<td>36.9 ± 20.6</td>
<td>36.4 ± 19.2</td>
</tr>
<tr>
<td><strong>Qmax (ml/sec)</strong></td>
<td>10.5 ± 2.6</td>
<td>10.3 ± 2.5</td>
<td>10.5 ± 2.5</td>
<td>10.6 ± 2.5</td>
</tr>
<tr>
<td><strong>PVR (ml)</strong></td>
<td>69.6 ± 82.1</td>
<td>69.2 ± 88.2</td>
<td>66.2 ± 80.0</td>
<td>67.5 ± 81.1</td>
</tr>
<tr>
<td><strong>PSA (ng/ml)</strong></td>
<td>2.3 ± 2.0</td>
<td>2.4 ± 2.1</td>
<td>2.4 ± 2.1</td>
<td>2.3 ± 1.9</td>
</tr>
<tr>
<td><strong>Creat (mg/dL)</strong></td>
<td>1.1 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>1.1 ± 0.1</td>
</tr>
</tbody>
</table>
Cumulative Incidence of BPH Progression: Placebo

Percent with Event

Years from Randomization

Placebo
Doxazosin
Finasteride
Combination
Cumulative Incidence of >4-Pt AUA Rise

Percent with Event

Years from Randomization

Placebo  Doxazosin  Finasteride  Combination

p < 0.0001 ; df = 3
Cumulative Incidence of AUR

p = 0.0034 ; df = 3

Percent with Event

Years from Randomization

Placebo  Doxazosin  Finasteride  Combination
Cumulative Incidence of BPH Invasive Therapy

- Placebo
- Doxazosin
- Finasteride
- Combination

Percent with Event

Years from Randomization

p < 0.0001 ; df = 3
Change in Prostate Volume at Year 4
Median Change in % from Baseline

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median Change</th>
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</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>18</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>18</td>
</tr>
<tr>
<td>Finasteride</td>
<td>-18</td>
</tr>
<tr>
<td>Combination</td>
<td>-13</td>
</tr>
</tbody>
</table>
Cumulative Incidence of BPH Progression Event By Subgroups of Baseline TRUS Volume

(Placebo Group)

TRUS ≥ 31 (ml)

TRUS < 31 (ml)

(P<0.001)
Cumulative Incidence of AUA Progression Event
By Subgroups of Baseline TRUS Volume

(Placebo Group)

Percent with Event

Time in Study (years)

TRUS ≥ 31 (ml)

TRUS < 31 (ml)

(P=0.042)
Cumulative Incidence of BPH Progression Event
By Subgroups of Baseline PVR
(Placebo Group)

Time in Study (years)

Percent with Event

- PVR ≥ 39 (ml)
- PVR < 39 (ml)

(P<0.001)
BPH Invasive Therapy

Prostate Volume Dependence

Cumulative Incidence (%)

Prostate Volume by TRUS (cc)

<20 20-40 >40

Placebo Dox Fin Comb

Cumulative Incidence (%)

Prostate Volume by TRUS (cc)

<20 20-40 >40

Placebo Dox Fin Comb
## Adverse Events (Sexual)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Plac</th>
<th>Dox</th>
<th>Fin</th>
<th>Comb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erectile Dysfunction</td>
<td>3.6</td>
<td>3.9</td>
<td>4.9*</td>
<td>5.6*</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.5</td>
<td>4.8*</td>
<td>2.5</td>
<td>5.9*</td>
</tr>
<tr>
<td>Postural Hypotension</td>
<td>2.5</td>
<td>4.4*</td>
<td>2.7</td>
<td>4.6*</td>
</tr>
<tr>
<td>Asthenia</td>
<td>2.2</td>
<td>4.5*</td>
<td>1.7</td>
<td>4.6*</td>
</tr>
<tr>
<td>Decreased Libido</td>
<td>1.5</td>
<td>1.7</td>
<td>2.5*</td>
<td>2.8*</td>
</tr>
<tr>
<td>Abnormal Ejaculation</td>
<td>0.9</td>
<td>1.2</td>
<td>1.9*</td>
<td>3.4*</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>0.7</td>
<td>1.0</td>
<td>0.8</td>
<td>1.4*</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0.6</td>
<td>1.0</td>
<td>0.6</td>
<td>1.3*</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0.4</td>
<td>0.9*</td>
<td>0.4</td>
<td>0.9*</td>
</tr>
<tr>
<td>Syncope</td>
<td>0.3</td>
<td>0.5</td>
<td>0.5</td>
<td>0.7*</td>
</tr>
</tbody>
</table>

* Higher compared to placebo at p <0.05
The number needed to treat (NNT) to prevent a case of overall progression is 8.4 for combination therapy, and 13.7 and 15.0 for Doxazosin and finasteride, respectively.

In patients with serum PSA > 4.0 ng/ml or baseline TRUS volume > 40 ml, the combination therapy NNTs are 4.7 and 4.9, respectively and 7.2 for both subgroups on finasteride therapy.
Important MTOPS Messages Beyond Combination Tx.

- MTOPS vs 1 yr Trials
- Study Characteristics
- Definition of Progression
- Event Risk Factors
- PSA vs. TRUS
- Importance of PVR
- Sexual Adverse Events
- Conclusions
Conclusions

• Most disease progression in the trial by symptom progression
• PSA, TRUS, AUA SI, Qmax, Age, and PVR all predict progression
• PVR important after all. Suspect even more important with larger values
• PSA surrogate for prostate volume
Surgical Therapy
Pressure/Flow Proved BOO
MINIMALLY INVASIVE BPH THERAPY: WHAT IS BEST?

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Why Minimally Invasive?
Is there something wrong with TURP?

- Designed to enhance patient comfort
- Reduced risk of complications
- Potentially reduced side effects
Classical Management
The Gold Standards

- TURP (Classical Loop)
- Vaportrode and later generations
- GYRUS (Bipolar and NaCl irrigant)
- TU/IP
Results of “Classical” Methods

• All remove tissue except TUIP
• Do not require special equipment
• Produce similar results
• TURP is “much less invasive” than reports from previous decades
AUASI vs Modality

Qmax vs Modality

Declining TURP Procedures
Medicare Population

Source: CMS Data c/o American Urological Association
Transurethral Incision of Prostate (TUIP)

- Lesser invasive procedure
- Can be performed in ASC setting
- Effective short term
- Low rate of retrograde ejaculation
Hyperthermia involves heating prostate tissue to $<45 \, ^\circ\text{C}$. Like post-procedure results, these devices have been short lived.

Thermotherapy generates intraprostatic temperatures of $>45 \, ^\circ\text{C}$.

Thermotherapy devices heat prostatic tissue to between 45 and $110 \, ^\circ\text{C}$.
Reasons for Selecting Thermotherapy

• More effective than medication
• Major complications uncommon relative to TURP
• Office procedure which does not require anesthesia and is often done simultaneous to other patient encounters
• Favored by reimbursement
TUMT - Transurethral Microwave Thermotherapy

• Microwaves used to heat and coagulate prostate tissue.

• Procedure takes 1/2 hour.

• Requires 2 to 7 days of catheterization.
Thermotherapy Procedure

ThermaMatrix Targis™

- Measurement of prostate length
- Consider block
- Urethral catheter and rectal probe placed
- 1/2 hour treatment
- Catheter placed or patient taught SIC
Microwave Thermotherapy
Conclusions

• Office based procedure
• Relatively free of major side-effects
• Significantly less durable than TURP
• Higher per procedure costs than other less invasive BPH treatments
AUASI vs Modality

Qmax vs Modality

TUNA™ - Transurethral Needle Ablation

- Delivers low level radio frequency energy into the prostate. Minimal urethral damage
- Performed with local anesthesia in an office setting
- Catheterization is 1-7 days
- Intended for men over age 50
Thermal Dosage

Dosage parameters vary depending upon the device and energy wavelength.

**TUNA**
- **TIME:** 2.3 min/lesion Prostiva
- **Area:** Small Footprint
- **Power:** 0–15 watts per electrode

**TUMT**
- **TIME:** 30 min/lesion
- **Area:** Large Footprint
- **Power:** 0–80 watts
TUNA™ Components
Radiofrequency Generator

- Pre-programmed setting
- Needle length adjusted to prostatic depth measured by ultrasound
- Lesion time:
  - 2 minutes 20 seconds Prostiva
- Target Tissue temperature 110°C (at lesion core)
- Urethral temperature <43°C
  - Alarms and 47°C Shutdown
TUNA™ COMPONENTS

Cartridge
AUASI vs Modality

Qmax vs Modality

TUNA Therapy History

>100,000 performed in 2010

U.S. Procedures/Year

- FDA Clearance
- Record Revenues
- Hospital Prospective Payment System (August 2000)
- Created Fee-Per-Use Hospital Model
- In-Office Reimbursement (January 2001)
Conclusions

• Newer minimally invasive treatments fill a useful niche. One time-hopefully-office based treatment for those with moderate LUTS and moderate bladder outlet obstruction

• These techniques are not as effective and durable as TURP at relieving bladder outlet obstruction
Conclusions II

• What is wrong with TURP? It is done in the OR and urologists are reimbursed 4 to 5 times as much when performing office based procedures.

• Minimally invasive BPH procedures will continue to overtake TURP as long as reimbursement schedules strongly favor the procedures.
AUASI vs Modality

Take Home Message

INTRODUCTION

• Primary bladder neck obstruction (PBNO) causes profound LUTS in men 20 -40 years old and historically been given erroneous diagnoses: “psychogenic voiding dysfunction”, “neurogenic bladder”, or “prostatitis.” (Blaivas and Norlen, 1984)
INTRODUCTION

• Videourodymanics is sine-qua non in the diagnosis of PBNO.

(Blaivas and Norlen, 1984)
INTRODUCTION

• Two-incision bladder neck incision is usually curative and durable, but often results in retrograde ejaculation (Trockman et al, 1996).

• Unilateral incision was adapted to preserve antegrade ejaculation (Webster et al, 1980; Norlen et al, 1986; Kaplan et al, 1994), but long-term outcomes are lacking.

• Our objective was to assess the success and long-term durability of single-incision TUIBN.
METHODS


• Evaluated for demographics, prostate size, presence of antegrade ejaculation, uroflometry, urodynamics and AUASS.
RESULTS

• All patients had UDS diagnosis of PBNO.
• Of 65 men treated, 34 men had preoperative uds data available.

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>(\alpha)-blocker use</td>
</tr>
<tr>
<td>Prostate size (grams)</td>
</tr>
<tr>
<td>Pdetqmax (cm H(_2)O)</td>
</tr>
<tr>
<td>Single-incision technique</td>
</tr>
<tr>
<td>Follow-up (months)</td>
</tr>
</tbody>
</table>
## RESULTS

### Table 2. Short-term outcomes (6 months)

<table>
<thead>
<tr>
<th></th>
<th>Mean Qmax (mL/s)</th>
<th>Mean PVR (mL)</th>
<th>Mean AUASS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-operative</td>
<td>11.07</td>
<td>93.52</td>
<td>22.13</td>
</tr>
<tr>
<td>3 month</td>
<td>18.13</td>
<td>67.76</td>
<td>12.85</td>
</tr>
<tr>
<td>6 month</td>
<td>17.00</td>
<td>62.50</td>
<td>9.50</td>
</tr>
<tr>
<td>p-value</td>
<td><strong>0.0119</strong></td>
<td>0.3308</td>
<td><strong>0.000047</strong></td>
</tr>
</tbody>
</table>

Significant improvement in Qmax and AUASS in short-term.
### RESULTS

<table>
<thead>
<tr>
<th></th>
<th>Mean Qmax (mL/s)</th>
<th>Mean AUASS</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-30 months</td>
<td>8.90</td>
<td>16.71</td>
</tr>
<tr>
<td>48-60 months</td>
<td>7.35</td>
<td>19.71</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td><strong>0.00046</strong></td>
<td></td>
</tr>
</tbody>
</table>

There is a significant rise in AUASS, which correlates with a drop in Qmax in the intermediate term.
RESULTS

- 87% maintained antegrade ejaculation
- No new complaints of ED
- Age, method of incision, and prostate volume had no effect on outcomes.

REPEAT SURGERY

- 7 (15%) repeat Transurethral Surgery at 32.4 months (11-65).
  - 4 double-incision TUIBN, 3 TURP
- 3 interstim placed at 45.3 months for refractory urgency.
CONCLUSIONS

• Largest series to date with longest follow-up of single-incision TUIBN for men with PBNO.
• Single-incision TUIBN provides short-term cure with preservation of AE.
• Recurrence of symptoms at 2 years
• Valuable option for sexually active males, yet counseling should be provided on limited durability.