Clinically and Statistically Significant Changes Seen in Sham Surgery Arms of Randomized, Controlled Benign Prostatic Hyperplasia Surgery Trials

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Abbreviations and Acronyms

BPH = benign prostatic hyperplasia

LUTS = lower urinary tract symptoms

Qmax = maximum urinary flow rate

RCT = randomized controlled trial

SS = symptom score

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Purpose: Medication trials frequently involve a placebo arm to more fairly assess the efficacy of the study drug. However, benign prostatic hyperplasia surgery trials rarely include a sham surgery group due to the inherent risks associated with simulating treatment in these patients. As a result the placebo response to sham surgery for benign prostatic hyperplasia is largely unknown.

Materials and Methods: We systematically reviewed the available literature to look for randomized, controlled trials involving endoscopic or intraprostatic injection benign prostatic hyperplasia treatments that included a sham surgical arm from January 1990 to February 2015. Studies that included an objective symptom questionnaire and maximum urinary flow at 3 months were included. Results were analyzed together with weighting based on study sample size.

Results: The initial search yielded a total of 1,998 potential studies. After reviewing abstracts and full text articles 14 randomized, controlled trials were included in some part. An average decrease from 22.3 to 16.7 (−27%) was seen in studies of the AUASS (American Urological Association symptom score) 3 months after a sham endoscopic procedure ($p = 0.0003$) with an increase in maximum urinary flow of 1.3 ml per second (14%, $p = 0.001$) at 3 months. Prostate injection based studies at 3 months were similar with a decrease from 21.3 to 15.7 (−26%, $p < 0.001$). Maximum urinary flow increased by 2.0 ml per second (23%, $p = 0.043$).

Conclusions: Sham controlled endoscopic and injection benign prostatic hyperplasia interventions demonstrate a considerable and statistically significant change in symptom scores and maximum urinary flow, which is comparable to the response seen in medication trials. Future uncontrolled benign prostatic hyperplasia surgical trials should consider these findings when interpreting outcomes.

Key Words: prostatic hyperplasia, lower urinary tract symptoms, endoscopy, injections, randomized controlled trials as topic

RANDOMIZED, placebo controlled clinical trials are considered the gold standard in research and yield level 1 evidence. While these trials are common in studies examining medications, they are less frequently seen in studies of patients undergoing surgical procedures. In medication trials a placebo medication is easy to manufacture and administer, creating an excellent comparative group with minimal additional risk to the

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patients taking placebo. The inclusion of this group is important as it serves as a reference point above which the study drug must exceed results to be considered effective.

However, assessing surgical outcomes is more challenging since creating a reasonable comparative placebo group is more difficult. As most surgical procedures are performed using some form of anesthesia and with a surgical incision, there is more risk associated with inclusion in a sham surgery group than with administration of a placebo medication. Uniform failure to account for the placebo effect leads one to assume that improvements in LUTS were related to treatment while the intervention effect remains unknown.

However, because endoscopic and intraprostatic injection BPH surgeries are done transurethrally or percutaneously and do not require a skin incision, some trials exist that include a sham surgery group that was evaluated with subjective and objective outcomes. In this study we sought to quantify the expected response to sham surgery for endoscopic procedures or intraprostatic injections for the treatment of LUTS related to BPH.

METHODS

A systematic review was done based on a literature search through the PubMed®-MEDLINE® database. The key words used to search were ("placebo" or "randomized controlled" or "sham") and ("prostatic hyperplasia" or "benign prostatic hyperplasia"). Search terms were chosen to be overly inclusive so that any potential relevant reports would be identified.

The literature search aimed to identify all full-length articles reporting the results of RCTs of surgery for LUTS due to BPH that were published between 1990 and February 2015. After screening titles and abstracts a first selection for eligibility was made (fig. 1). The reference list of applicable RCTs was screened for additional references. Review articles and book chapters on BPH were also searched to look for additional studies. Only RCTs including a sham procedure (ie catheter insertion, antenna insertion to simulate microwave therapy, or intraprostatic injection of placebo or vehicle) for LUTS due to BPH were considered.

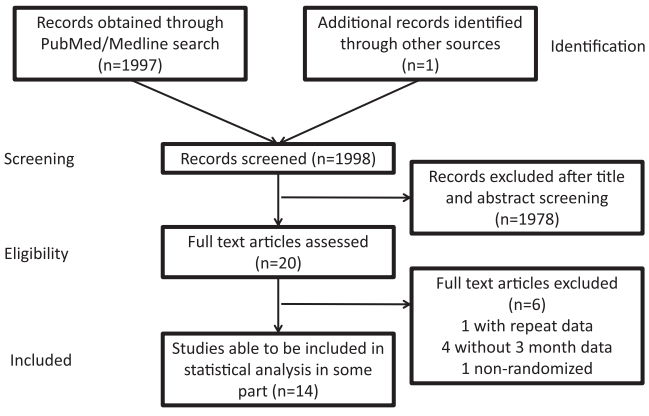

Figure 1.

Once selected the articles were studied in full text to gather information about study design, baseline assessments of the study metric (questionnaire based SSs and Qmax) and reassessment of these outcomes at some later interval. To create standardization studies were only analyzed if they included outcome data on 3 months after the sham procedure or intervention. When data were missing from articles that could otherwise be included, investigators[1,2] or device manufacturers[3] were contacted to obtain this missing information. In some cases missing results were pulled from the NIH (National Institutes of Health) website (ClinicalTrials.gov).[4–6]

Studies were excluded from data analysis on SS if they did not report relevant data about main functional outcomes, including well recognized SSs such as AUASS, Madsen-Iversen SS or Boyarksy SS. If studies did not include accepted SS outcomes, they were still included in Qmax calculations if these data were available. In a separate calculation for SS articles that reported outcomes only with a study that used a 0 to 27 scale (Boyarsky and Madsen-Iversen SSs) were scaled to a 0 to 35 scale similar to AUASS and analyzed together.

Studies were then separated based on whether they were for intraprostatic injection or mimicked endoscopic treatment of BPH. These different groups were analyzed separately as intraprostatic injections may have had a different placebo effect (mass effect from drug, or trauma to prostate parenchyma or capsule from needle insertion), which could cause local changes in the prostate that would differ from those of an endoscopic procedure.

Data organization and statistical analysis were completed with Excel®. Weighted means of SS and Qmax were calculated using reported means with weights determined by the number of patients in each study. The p values of changes were determined by the paired t-test comparing before and after differences, which were again weighted by the number of patients. Outcomes were considered statistically significant at $p < 0.05$. Forest-type plots were constructed based on these findings. In these plots the relative size of the diamond depicted was scaled to the number of patients examined in the respective study with a standard effect size added to the right side of the figure.

RESULTS

A PubMed-MEDLINE database search using the selected key words yielded 1,997 results (fig. 1). One additional and potentially relevant record was found based on a review of book chapters. After reviewing the titles and abstracts of these studies 1,978 were excluded as they did not meet initial study inclusion criteria due to a variety of reasons (ie not sham controlled or trials were for medical treatment of BPH). Full text articles of the remaining 20 studies were then reviewed. Four articles were excluded