The Efficacy and Safety of Combined Therapy with α-Blockers and Anticholinergics for Men with Benign Prostatic Hyperplasia: A Meta-Analysis

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Purpose: We performed a meta-analysis to compare treatment with α-blockers and anticholinergics (ie combination therapy) to α-blocker monotherapy to clarify the efficacy and safety of this treatment approach among men with storage urinary symptoms related to benign prostatic hyperplasia.

Materials and Methods: We searched for trials of men with benign prostatic hyperplasia/lower urinary tract symptoms that were randomized to combination treatment or α-blockers alone. We pooled data from 7 placebo controlled trials meeting inclusion criteria. Primary outcomes of interest included changes in International Prostate Symptom Score (storage subscores) and urinary frequency. We also assessed post-void residual volume, maximal flow rate and the incidence of urinary retention. Data were pooled using random effects models for continuous outcomes and the Peto method to generate odds ratios for acute urinary retention.

Results: Combination therapy had a significantly greater reduction in International Prostate Symptom Score storage subscores (Δ −0.73, 95% CI −1.09 − −0.37) and voiding frequency (Δ −0.69 voids, 95% CI −0.97 − −0.41). There was also a greater reduction in maximal urinary flow rate (Δ −0.59 ml per second, 95% CI −1.04 − −0.14) and increase in post-void residual urine volume (Δ 11.60 ml, 95% CI 8.50−14.70) with combination therapy. The number needed to treat with combination therapy to cause 1 acute urinary retention episode was 101 (95% CI 60−267).

Conclusions: Combination treatment with α-blockers and anticholinergics significantly improved storage voiding parameters compared to men treated with α-blocker therapy alone. This treatment approach is safe with a minimal risk of increased post-void residual urine volume, decreased maximal urinary flow rate or acute urinary retention.

Abbreviations and Acronyms

AUR = acute urinary retention

BPH = benign prostatic hyperplasia

CO = combination therapy

ER = extended release

I-PSS = International Prostate Symptom Score

LUTS = lower urinary tract symptoms

PVR = post-void residual urine volume

Qmax = maximal urinary flow rate

RCT = randomized clinical trial

WMD = weighted mean difference

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Editor's Note: This article is the fourth of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 2316 and 2317.

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To date, established medical interventions for men with LUTS associated with benign prostatic hyperplasia/enlargement (eg α-blockers and 5α-reductase inhibitors) have focused on the obstructive aspect of patients' symptoms. However, more than 40% of men have a significant storage component to their symptoms and 16% exhibit symptoms of an overactive bladder.[1,2] This suggests that anticholinergics may have a role in symptom amelioration in certain men with BPH/LUTS.

Indeed, prior randomized controlled trials have demonstrated the efficacy of combination therapy with α-blockers and anticholinergics.[3,4] However, existing trials report a variety of outcomes with inconsistent findings. Furthermore, population based data suggest that anticholinergic therapy is rarely used to treat men with BPH, with less than 3% of receiving anticholinergics.[5] This infrequent use is widely held to be driven by fears of exacerbation of obstructive symptoms and urinary retention in an elderly population with BPH.

To better define the efficacy and safety of this treatment approach, we performed a meta-analysis of randomized clinical trials to quantify the effects of combination therapy (ie anticholinergic medication in addition to an α-blocker) compared to α-blocker monotherapy.

MATERIALS AND METHODS

Eligibility Criteria

Following the guidelines from the Quality of Reporting of Meta-Analyses conference,[6] we established inclusion criteria before our search. We planned to include only placebo controlled, RCTs of men with BPH that compared combination therapy to α-blocker monotherapy. We excluded studies examining medical therapy for men who were treated with surgery for BPH. We excluded observational studies without a control group, those evaluating anticholinergic monotherapy and trials where the control group only received placebo.

Search Strategy

We searched MEDLINE®, Pre-MEDLINE, the Cochrane Register of Controlled Trials, EMBASE and ClinicalTrials.gov databases for trials of interest. We considered all publications in any language published before September 12, 2012. Our search strategy combined and exploded terms for "benign prostatic hyperplasia," "bladder outlet obstruction," "anticholinergics" and "antimuscarinics". We also included specific generic and trade drug names in our search. We contacted major drug companies regarding recently completed trials for which data were available. We reviewed the references of selected randomized trials to identify other publications potentially missed by our initial search.

Study Selection

Quality of the randomized trials was assessed based on method of randomization, allocation concealment, blinding, evidence of selective reporting, rates of completion of assigned intervention and the group used for final statistical analysis (ie full analysis set vs intent to treat).[7] We included studies that were deemed high quality by consensus between study authors.

Outcomes of Interest and Data Extraction

The primary outcomes of interest were changes in the I-PSS storage subscores and urinary frequency, which both reflect storage LUTS among men with BPH.[8] Secondary outcomes of interest included Qmax, PVR and the incidence of AUR. Data were abstracted using a standardized form and inconsistencies with data were discussed until consensus was reached with study authors. We attempted to contact study authors to clarify questions on study design or to supplement missing data from individual publications.

Statistical Analysis

For continuous outcomes, the effect size of interest was the difference in pre-intervention and post-intervention mean scores or values (ie weighted mean difference). One trial with 2 intervention arms with varied doses had the respective means and standard deviations pooled for comparison to the control group.[9] Missing standard deviations for pretreatment and posttreatment mean values were imputed by using the arithmetic mean of available standard deviations.[10] Missing standard deviations for change scores were calculated using pre-intervention and post-intervention means and standard deviations, with a correlation coefficient of 0.5.[11] Due to clinical differences between RCTs (ie medication types, inclusion criteria) we pooled WMDs using DerSimonian and Laird random effects models.[12] As AUR and urethral catheterization were rare events, we used the Peto method of calculating odds ratios for both of these dichotomous outcomes.[13]

Statistical heterogeneity was assessed with the I^2 statistic, which measures the proportion of inconsistency in individual studies not explained by chance.[14] To assess for publication bias, funnel plots were created for each outcome and qualitatively assessed. Influence analyses assessed whether significant findings were affected by exclusion of individual trials. Sensitivity analyses were carried out with variations of the correlation coefficient (ie $r = 0.0$, 0.25 and 0.80). Subgroup analyses were planned a priori and performed to try to understand statistical heterogeneity between trials. As prior exposure to α-blockers may influence treatment effect, we stratified our forest plots based on this variable. All tests were