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Review – Voiding Dysfunction

α1-Blockers Improve Benign Prostatic Obstruction in Men with Lower Urinary Tract Symptoms: A Systematic Review and Meta-analysis of Urodynamic Studies

Ferdinando Fusco [a,*], *Alessandro Palmieri* [a], *Vincenzo Ficarra* [b,c], *Gianluca Giannarini* [c], *Giacomo Novara* [d], *Nicola Longo* [a], *Paolo Verze* [a], *Massimiliano Creta* [e], *Vincenzo Mirone* [a]

[a] *Urology Unit, Department of Neurosciences, Science of Reproduction and Odontostomatology, University of Naples Federico II, Naples, Italy;* [b] *Urology Unit, Department of Experimental and Clinical Medical Sciences, University of Udine, Udine, Italy;* [c] *Urology Unit, Academic Hospital Santa Maria della Misericordia, Udine, Italy;* [d] *Urology Unit, Department of Surgery, Oncology, and Gastroenterology, University of Padua, Padua, Italy;* [e] *Urology Unit, Buon Consiglio Fatebenefratelli Hospital, Naples, Italy*

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Abstract

Context: The urodynamic outcomes for α1-blockers (ABs) treatment in patients with lower urinary tract symptoms related to benign prostatic enlargement (LUTS/BPE) is a matter of debate.
Objective: To perform a systematic review and meta-analysis of studies evaluating the ABs urodynamic outcomes in patients with LUTS/BPE. The primary endpoint was variation in bladder outlet obstruction index (BOOI). Secondary endpoints were the maximum urinary flow rate (Q_{max}) and detrusor pressure at Q_{max} ($P_{det}Q_{max}$). A meta-analysis of placebo-controlled randomized clinical trials (RCTs) was performed to compare ABs with placebo.
Evidence acquisition: A systematic review of PubMed/Medline, ISI Web of Knowledge, and Scopus databases was performed in May 2015. Seventeen studies were selected for inclusion.
Evidence synthesis: The overall pooled data showed a mean BOOI change of −14.19 ($p < 0.0001$), a mean $P_{det}Q_{max}$ change of −11. 39 cm H_2O ($p < 0.0001$), and a mean Q_{max} improvement of 2.27 ml/s ($p < 0.0001$). Subgroup analysis showed a mean BOOI change of −14.88 ($p = 0.01$) for alfuzosin, −19.41 ($p = 0.01$) for doxazosin, −16.47 ($p < 0.0001$) for naftopidil, −30.45 ($p < 0.0001$) for silodosin, −14.27 ($p = 0.002$) for tamsulosin, and −6.69 ($p = 0.005$) for terazosin. Subanalysis of RCTs containing a placebo arm showed a significant improvement in BOOI in patients undergoing ABs treatment. Meta-regression revealed a significant positive association between the percentage of patients with obstruction at baseline and the improvement in BOOI after treatment with ABs.
Conclusion: ABs improve BOOI in patients with LUTS/BPE mainly by reducing $P_{det}Q_{max}$, and this effect is higher in patients presenting with urodynamic obstruction at baseline. The free Q_{max} variation underestimates the real effect of ABs on benign prostatic obstruction.
Patient summary: Results of this meta-analysis suggest that α1-blockers objectively improve urinary voiding function in patients with benign prostatic obstruction.

* Corresponding author. Urology Unit, Department of Neurosciences, Science of Reproduction and Odontostomatology, University of Naples Federico II, Via S. Pansini 5, 80131 Naples, Italy.
Tel. +39 081 7462504; Fax: +39 081 5452959.
E-mail address: ferdinando-fusco@libero.it (F. Fusco).

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1. Introduction

α1-Blockers (ABs) are frequently prescribed as first-line therapy for the treatment of moderate to severe lower urinary tract symptoms related to benign prostatic enlargement (LUTS/BPE) [1,2]. To date, six ABs have been approved for the treatment of LUTS/BPE: terazosin, doxazosin, tamsulosin, naftopidil, alfuzosin, and silodosin. All of them have been reported to significantly improve voiding and storage LUTS with respect to placebo [2]. Historically, it has been assumed that the pathophysiology of LUTS/BPE is the result of benign prostatic obstruction (BPO). Consequently, it was generally presumed that LUTS/BPE improvements on ABs treatment were due to a reduction in BPO mediated by relaxation of prostatic smooth muscle. In recent years, various lines of evidence have questioned this paradigm. Studies have underlined that symptom score, peak urinary flow rate at free uroflowmetry (free Q_{max}), and BPO represent different aspects of LUTS that are only poorly related to each other [3]. Published data support the common belief that ABs have a minimal effect on urinary flow rate and therefore a minimal impact on BPO [2]. It has also been hypothesized that the mechanisms underlying the beneficial effects of ABs may be more complex than previously assumed, and that α1-adrenoceptors located outside the prostate (eg, urinary bladder and/or spinal cord) may play a role [4]. However, BPO remains a key issue when dealing with patients with BPE. A correct diagnosis of BPO requires an invasive pressure/flow study (PFS) in which urodynamic Q_{max} and detrusor pressure at Q_{max} ($P_{det}Q_{max}$) are measured and used to calculate the bladder outlet obstruction index (BOOI). Obstruction is defined as a high-pressure/low-flow micturitional pattern and is diagnosed when the BOOI is >40. Although the BOOI is recommended for measuring the level of obstruction, most studies evaluating therapy with ABs for LUTS/BPE confined analyses to free uroflowmetry, symptom score, and postvoid residual urine (PVR) [5,6]. Conversely, only a few high-quality studies have evaluated the urodynamic outcomes of AB treatment for PFS parameters in patients suffering from LUTS/BPE, and the results have been inconclusive [3,5]. We performed a meta-analysis of published studies to clarify the urodynamic outcomes of ABs treatment on BOOI and other major PFS urodynamic parameters in patients with LUTS/BPE.

2. Evidence acquisition

This analysis was conducted and reported according to the general guidelines recommended by the Primary Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [7].

2.1. Data sources and searches

In May 2015 we used the National Library of Medicine PubMed search engine, the Scopus database, and the ISI Web of Knowledge official website to search for all published studies evaluating urodynamic measurement of BOOI in LUTS/BPE patients before and after AB therapy. The followings search strings were used: tamsulosin AND urodynamics; silodosin AND urodynamics; alfuzosin AND urodynamics; doxazosin AND urodynamics; naftopidil AND urodynamics; and terazosin AND urodynamics. We included publications that met the following criteria: reporting original research; English language; human studies; enrolling LUTS/BPE patients; and reporting Q_{max} and $P_{det}Q_{max}$ evaluated by PFS before and after treatment with an AB. Reference lists in relevant articles and reviews were also screened for additional studies. Abstracts (with no subsequent full-text publications) and unpublished studies were not considered. Two authors (F.F., M.C.) reviewed the records separately to select relevant publications, with any discrepancies resolved by open discussion. The quality of the randomized controlled trials (RCTs) was assessed using the Jadad score [8].

2.2. Data extraction

The following data were extracted from the studies included: publication year; study design; sample size; number of patients with obstruction at baseline; type of AB used; duration of treatment; and $P_{det}Q_{max}$ and Q_{max} values at baseline and after treatment. $P_{det}Q_{max}$ and Q_{max} values at baseline and after treatment were also extracted from the placebo arms when available. BOOI was calculated using the formula BOOI = $P_{det}Q_{max} - 2Q_{max}$ [6]. The number and percentage of patients with obstruction at baseline who changed their class of obstruction from "obstructed" to "non-obstructed" or "equivocal" was also extracted.

2.3. Outcomes of interest

The primary outcome was change in BOOI. Changes in $P_{det}Q_{max}$ and Q_{max} were evaluated as secondary outcomes.

2.4. Statistical methods

Continuous variables are reported as mean difference (MD) estimate, standard error, inverse-variance weight, and 95% confidence intervals (CIs) for each study. Statistical pooling for MD estimates was performed according to a random-effects model with generic inverse-variance weighting, computing estimates with 95% CI, using Review Manager Software 5 (The Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark). Study bias was appraised by graphical inspection of funnel plots. Hypothesis testing for superiority was set at a two-tailed level of 0.05. Hypothesis testing for statistical homogeneity was set at a two-tailed level of 0.10 and was based on the Cochran Q test, with I^2 values of 25%, 50%, and 75% representing mild, moderate, and extensive statistical inconsistency, respectively. Forest plots were generated to show changes in BOOI, Q_{max}, and $P_{det}Q_{max}$ during the assumption of AB versus baseline. For the placebo-controlled RCTs, a forest plot was also generated showing the change in BOOI during the