EUROPEAN UROLOGY XXX (2017) XXX–XXX

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Stone Disease

Editorial by XXX on pp. x–y of this issue

Efficacy and Safety of Tamsulosin in Medical Expulsive Therapy for Distal Ureteral Stones with Renal Colic: A Multicenter, Randomized, Double-blind, Placebo-controlled Trial

Zhangqun Ye [a,b,†], Guohua Zeng [c,†], Huan Yang [a,b,†], Kun Tang [a,b,†], Xiaochun Zhang [d], Hong Li [e], Weibing Li [f], Zhong Wu [g], Lingwu Chen [h], Xingfa Chen [i], Xiankui Liu [j], Yaoliang Deng [k], Tiejun Pan [l], Jinchun Xing [m], Shusheng Wang [n], Yue Cheng [o], Xiaojian Gu [p], Wenxi Gao [q], Jianggen Yang [r], Yonghai Zhang [s], Qiwu Mi [t], Lin Qi [u], Jiongming Li [v], Weilie Hu [w], Peiyu Liang [x], Zhaolin Sun [y], Changbao Xu [z], Yongfu Long [aa], Yongbin Liao [bb], Siping Liu [cc], Guoqing Liu [dd], Xun Xu [ee], Wei He [a,b], Zhiqiang Chen [a,b,], Hua Xu [a,b,*]*

[a] *Department of Urology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China;* [b] *Hubei Institute of Urology, Wuhan, China;* [c] *The Center of Minimally-invasive Surgery, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China;* [d] *The Institute of Urology, Peking University, Beijing, China;* [e] *Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Chengdu, China;* [f] *Department of Urology and Nephrology, The Third Affiliated Hospital of Chongqing Medical University, Chongqing, China;* [g] *Department of Urology, Huashan Hospital of Fudan University, Shanghai, China;* [h] *Department of Urology, the First Affiliated Hospital of Zhongshan University, Guangzhou, China;* [i] *Department of Urology, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China;* [j] *Department of Urology, the First Affiliated Hospital of Chinese Medical University, Shenyang, China;* [k] *Department of Urology, the First Affiliated Hospital of Guangxi Medical University, Nanning, China;* [l] *Department of Urology, Wuhan General Hospital of Guangzhou Military Region, Wuhan, China;* [m] *Department of Urology, the First Affiliated Hospital of Xiamen University, Xiamen, China;* [n] *Department of Urology, Guangdong Provincial Hospital of Traditional Chinese Medicine, Guangzhou, China;* [o] *Department of Urology, the First People's Hospital of Ningbo City, Ningbo University Medical School, Ningbo, China;* [p] *Department of Urology, JiangSu Province Hospital of Traditional Chinese Medicine, Nanjing, China;* [q] *Department of Urology, Hubei Provincial Hospital of Traditional Chinese Medicine, Wuhan, China;* [r] *Department of Urology, the People's Hospital of Shenzhen, Shenzhen, China;* [s] *Department of Urology, Shantou Central Hospital, Shantou, China;* [t] *Department of Urology, the People's Hospital of Dongguan, Dongguan, China;* [u] *Department of Urology, Xiangya Hospital of Centra South University, Changsha, China;* [v] *Department of Urology, the Second Affiliated Hospital of Kunming Medical University, Kunming, China;* [w] *Department of Urology, Guangzhou General Hospital of Guangzhou Military Region, Guangzhou, China;* [x] *Department of Urology, the Affiliated Hospital of Hainan Medical College, Haikou, China;* [y] *Department of Urology, the People's Hospital of Guizhou Province, Guiyang, China;* [z] *Department of Urology, the Second Affiliated Hospital of Zhengzhou University Medical School, Zhengzhou, China;* [aa] *Department of Urology, Shaoyang Central Hospital, Shaoyang, China;* [bb] *Department of Urology, Jiangmen Hospital of Zhongshan University, Jiangmen, China;* [cc] *Department of Urology, Meizhou Hospital of Zhongshan University, Meizhou, China;* [dd] *Department of Urology, Foshan Maternal and Child Health Care Hospital of Nanfang Medical University, Foshan, China;* [ee] *Department of Urology, Nanhai Hospital of Nanfang Medical University*

[†] These authors contributed equally to this work.
[*] Corresponding authors. Department of Urology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China. Tel. +86-27-83663454; Fax: +86-27-83663454.
E-mail addresses: zhqchen8366@163.com (Z. Chen), xuhuawhu@163.com (H. Xu).

https://doi.org/10.1016/j.eururo.2017.10.033

Please cite this article in press as: Ye Z, et al. Efficacy and Safety of Tamsulosin in Medical Expulsive Therapy for Distal Ureteral Stones with Renal Colic: A Multicenter, Randomized, Double-blind, Placebo-controlled Trial. Eur Urol (2017), https://doi.org/10.1016/j.eururo.2017.10.033

Article info

Article history:
Accepted October 26, 2017

Associate Editor:
J.-N. Cornu

Statistical Editor:
Andrew Vickers

Keywords:
Adrenergic alpha blockers
Medical expulsive therapy
Tamsulosin
Distal ureteral stones
Renal colic

Abstract

Background: Recent large high-quality trials have questioned the clinical effectiveness of medical expulsive therapy using tamsulosin for ureteral stones.
Objective: To evaluate the efficacy and safety of tamsulosin for distal ureteral stones compared with placebo.
Design, setting, and participants: We conducted a double-blind, placebo-controlled study of 3296 patients with distal ureteral stones, across 30 centers, to evaluate the efficacy and safety of tamsulosin.
Intervention: Participants were randomly assigned (1:1) into tamsulosin (0.4 mg) or placebo groups for 4 wk.
Outcome measurements and statistical analysis: The primary end point of analysis was the overall stone expulsion rate, defined as stone expulsion, confirmed by negative findings on computed tomography, over a 28-d surveillance period. Secondary end points included time to stone expulsion, use of analgesics, and incidence of adverse events.
Results and limitations: Among 3450 patients randomized between September 1, 2011, and August 31, 2013, 3296 (96%) were included in the primary analysis. Tamsulosin benefits from a higher stone expulsion rate than the placebo (86% vs 79%; $p < 0.001$) for distal ureteral stones. Subgroup analysis identified a specific benefit of tamsulosin for the treatment of large distal ureteral stones (>5 mm). Considering the secondary end points, tamsulosin-treated patients reported a shorter time to expulsion ($p < 0.001$), required lower use of analgesics compared with placebo ($p < 0.001$), and significantly relieved renal colic ($p < 0.001$). No differences in the incidence of adverse events were identified between the two groups.
Conclusions: Our data suggest that tamsulosin use benefits distal ureteral stones in facilitating stone passage and relieving renal colic. Subgroup analyses find that tamsulosin provides a superior expulsion rate for stones >5 mm, but no effect for stones ≤5 mm.
Patient summary: In this report, we looked at the efficacy and safety of tamsulosin for the treatment of distal ureteral stones. We find that tamsulosin significantly facilitates the passage of distal ureteral stones and relieves renal colic.

1. Introduction

Medical expulsive therapy (MET) refers to the administration of drugs such as tamsulosin, an α-adrenoceptor antagonist, to relax the smooth muscle of the ureter and inhibit peristaltic activity [1,2]. The efficacy of tamsulosin has been evaluated in numerous randomized controlled trials (RCTs) [2–6], with several meta-analyses having been published [7–9]. In general, trials have supported the use of tamsulosin to achieve higher stone expulsion rates and lower analgesic requirements. In our previous study, we demonstrated a significant therapeutic benefit of tamsulosin, over nifedipine, for relieving renal colic and facilitating ureteral stone expulsion [10].

Nevertheless, several recently published high-quality and large RCTs have questioned the effectiveness of α-blockers to be ineffective for the management of ureteral stones [11,12]. The Spontaneous Urinary Stone Passage Enabled by Drugs (SUSPEND) trial established that neither tamsulosin nor nifedipine decreased the need for further treatment to achieve stone clearance in 4 wk compared with placebo [11]. Additionally, a phase III trial, which included multiple centers, reported no benefit of tamsulosin for patients with distal ureteral calculi with regard to spontaneous stone passage, time to stone expulsion, or analgesic requirement [12]. Interestingly, another RCT, using silodosin, provided evidence of a possible benefit of silodosin in patients with distal ureteral stones [13]. In addition, the 2017 European Association of Urology guidelines recommend the use of α-blockers for MET as one of the treatment options, in particular for (distal) ureteral stones >5 mm [14].

The contradictory results provided by meta-analyses of small RCTs versus the findings of large, multicenter trials have questioned the effectiveness of tamsulosin. To address this issue, we conducted a multicenter, randomized, double-blind, placebo-controlled trial, including 3296 distal ureteral stone patients with renal colic, across 30 centers in China, to evaluate the efficacy and safety of tamsulosin as medical expulsion therapy for distal ureteral stones.

2. Patients and methods

2.1. Study design and participants

This double-blind, randomized, placebo-controlled trial was designed by urologists from the Urolithiasis Group of the Chinese Urological Association and researchers at Astellas Pharma (the study sponsor and manufacturer of the placebo). Data were analyzed by investigators at Tongji Hospital, Huazhong University of Science and Technology. The trial protocol and the informed consent form were approved by the

Please cite this article in press as: Ye Z, et al. Efficacy and Safety of Tamsulosin in Medical Expulsive Therapy for Distal Ureteral Stones with Renal Colic: A Multicenter, Randomized, Double-blind, Placebo-controlled Trial. Eur Urol (2017), https://doi.org/10.1016/j.eururo.2017.10.033