Chapter 7

Medical Expulsive Therapy in Urolithiasis: Evidence-Based Applications of Alpha Blockers and Calcium Channel Blockers in Calculi

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Abstract

Background: Minimally invasive treatments of urolithiasis, including extracorporeal shock wave lithotripsy, ureteroscopy, and percutaneous nephrostolithotomy, have very high efficacy with high cost. The use of medical expulsive therapy (MET) offers a non-surgical and cost-effective alternative to the management of the rightly chosen patient with ureteral calculi.

Objective: The purpose of the review is to summarize the modern literature related to MET, as well as providing clinicians with recommendations on the rational use of MET in the treatment of stone disease.

Methods: A systematic review of clinical trials, meta-analyses, and AUA/EAU guidelines was conducted to evaluate the effectiveness and safety of medical expulsive therapies suggested, including, calcium channel blockers, corticosteroids, and adrenergic α -adrenoceptor antagonists.

Results: AUA/EAU guidelines have confirmed medical expulsive therapy (MET) as a valuable reatment alternative in the management of selected patients. The α-adrenoceptor antagonist and calcium channel blockers have been shown to have a higher success rate in stone-expulsion, with the former proving to be more effective than the latter. Specifically nifedipine and other alpha-antagonists of adrenergic nature have been confirmed as clinically effective, safe and well tolerated. Moreover, it has also been shown that MET also decreases the number of colic bouts, narcotic use, and hospitalization, thus decreasing the number of healthcare expenses and eliminating unnecessary surgical operations.

Conclusion: MET is a very effective therapeutic modality in the right selected patient, especially the ones who present with distal ureteral calculi of about 1cm in diameter and is considered to have the option of being managed on observational basis. Even though there is a solid amount of supporting evidence, MET has not been applied clinically to the best of its abilities. The additional contribution of the alpha-adrenergic antagonists and calcium channels blockers include the increased stone clearance rates and analgesic effects in the patients receiving alternative treatments, including shock wave lithotripsy and ureteroscopy.

Keywords: Kidney; stones; urolithiasis, alpha blockers , calcium channel blockers.

1. Introduction

Urinary stone disease is a prevalent pathological condition that commonly presents with acute severe pain when calculi become lodged in the ureter, frequently necessitating emergency department evaluation.[12] The global prevalence of nephrolithiasis is estimated at

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approximately 10%, with a significant lifetime recurrence rate, placing a substantial burden on healthcare systems worldwide.[1]

The use of medical expulsive therapy (MET), which encompasses alpha-adrenergic antagonists, corticosteroids, and calcium channel blockers, has been extensively reported to facilitate spontaneous passage of ureteral calculi in patients who do not require urgent urologic intervention.[2,3] The American Urological Association (AUA) and the European Association of Urology (EAU) broadly recommend that patients diagnosed with ureteral stones less than 10 mm in diameter who do not require urgent care should receive pharmacologic therapy to facilitate stone passage.[4,5]

An extensive multicenter trial evaluating tamsulosin versus nifedipine in subjects with ureteral stones of any location and size up to 10 mm has contributed important evidence to this clinical debate.[6] Two subsequent meta-analyses have further elucidated the role of MET in ureteral stone management; both identified compelling evidence that tamsulosin and other alpha-blockers are effective and should be prescribed to patients with stones measuring 5–10 mm.[7,8]

Prior research estimated MET utilization rates between 1.1% and 14% among emergency physicians managing urolithiasis patients, suggesting a significant knowledge translation gap that adversely affects patient outcomes and healthcare costs.[10] These studies documenting MET underutilization are limited, however, in their capacity to measure the appropriateness of MET prescribing with respect to alpha-blocker selection.

1.1 Objective

Medical expulsive therapy represents an established, pharmacologically based, and cost-effective intervention for ureteral

calculi. Alpha-adrenergic antagonists and calcium channel blockers are the most efficacious pharmacologic agents for facilitating stone passage and constitute the primary treatment recommended by current AUA and EAU guidelines.[3,4] Nevertheless, MET is not uniformly applied across clinical settings, and evidence-based guidance on its correct implementation remains incompletely disseminated.

This review aims to:

- Establish the pharmacological and pathophysiological rationale for MET, including the mechanisms by which alpha-blockers and calcium channel blockers relax ureteral smooth muscle, modulate peristalsis, and reduce intraluminal pressure.
- Systematically evaluate the clinical evidence supporting alpha-adrenergic antagonists — including tamsulosin, silodosin, alfuzosin, terazosin, and doxazosin — as MET agents, with reference to landmark randomized controlled trials (RCTs), Cochrane reviews, and contemporary meta-analyses.
- Evaluate clinical evidence for calcium channel blockers, primarily nifedipine, as an alternative or adjunctive MET strategy, including mechanistic rationale, RCT data, and current limitations.
- Synthesize high-quality evidence and guideline consensus to support clinical decision-making regarding MET pharmacological interventions.

2. Methods

To determine the effectiveness and safety of MET in ureteral stones, a systematic review of clinical trials, meta-analyses, and guidelines

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published by the AUA and EAU was performed.[3,4] The review concentrated particularly on calcium channel blockers, corticosteroids, and adrenergic α-adrenoceptor antagonists, their mechanisms of facilitating stone passage, and their safety profiles. Electronic databases searched included PubMed/MEDLINE, Embase, and the Cochrane Library, using the terms: urolithiasis, ureteral calculi, medical expulsive therapy, tamsulosin, alpha-blocker, nifedipine, calcium channel blocker, corticosteroid, stone expulsion, and spontaneous passage.

Inclusion criteria encompassed RCTs, prospective cohort studies, and systematic reviews/meta-analyses published between 2000 and 2024, reporting on stone expulsion rates, time to passage, analgesic requirements, surgical intervention rates, and adverse effects. Studies were assessed for quality using the Cochrane Risk of Bias tool for RCTs and the AMSTAR-2 checklist for meta-analyses.

Treatment of ureteral stones has been transformed by the recognition that most stones — particularly those in the distal ureter measuring less than 10 mm — may pass spontaneously.[9] MET has therefore emerged as a conservative first-line strategy aimed at facilitating stone passage with minimal procedural intervention. The primary mechanism of pharmacologic agents employed in MET is relaxation of ureteral smooth muscle, reduction of spasms, and enhancement of peristaltic coordination, collectively increasing the probability of spontaneous stone expulsion.[13]

3. Pharmacology Of Medical Expulsive Therapy

3.1 Alpha-Adrenergic Receptor Antagonists

The most extensively studied pharmacologic agents in MET are the α-adrenergic receptor antagonists, owing to their specific effect on

ureteral smooth muscle.[7] α1-Adrenergic receptors — particularly the α1A and α1D subtypes — are highly concentrated in the distal ureter and play a central role in regulating ureteral contractility.[13] Agents including tamsulosin, silodosin, alfuzosin, and doxazosin have been evaluated across numerous RCTs. These drugs reduce ureteral tone and peristaltic frequency while decreasing intraluminal pressure, collectively facilitating stone passage.[14]

Multiple meta-analyses have demonstrated that α-blockers significantly increase stone expulsion rates and shorten time to passage, with the most pronounced benefit observed for distal ureteral stones greater than 5 mm in diameter.[7,8] Tamsulosin (0.4 mg daily) remains the most widely studied and most commonly prescribed agent in this class, demonstrating consistent efficacy across heterogeneous patient populations.[6]

3.2 Calcium Channel Blockers

Calcium channel blockers represent a secondary pharmacologic class considered in MET. These drugs attenuate calcium influx into smooth muscle cells by blocking L-type calcium channels, thereby inhibiting ureteral smooth muscle contraction.[15] Nifedipine has been the most extensively studied agent in this category. Although early trials demonstrated promising results, subsequent comparative studies and systematic reviews indicate that calcium channel blockers are modestly less effective than α-adrenergic antagonists and have been progressively de-emphasized in current clinical practice.[5,8]

3.3 Corticosteroids

Corticosteroids have been investigated as adjunctive agents in MET based on their anti-inflammatory properties. Ureteral obstruction by a calculus induces mucosal edema and local inflammation that may

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impede spontaneous passage.[16] Short courses of prednisolone, administered in combination with alpha-blockers, have been evaluated for their capacity to reduce ureteral edema and potentially enhance pharmacologic efficacy. While some studies report improved expulsion rates with combination therapy, the adverse-effect profile of systemic corticosteroids does not support their routine use.[16]

4. Results

4.1 Stone Expulsion Rates and Clinical Outcomes

AUA and EAU guidelines confirm MET as a valuable treatment alternative for appropriately selected patients.[3,4] Both alpha-adrenoceptor blockers and calcium channel blockers have demonstrated superiority over placebo in facilitating stone passage, with alpha-blockers consistently outperforming calcium channel blockers.[7,8] Nifedipine and alpha-adrenergic antagonists have been confirmed as clinically effective, safe, and well tolerated across diverse patient populations.[6]

The effectiveness of MET is significantly influenced by stone size and anatomical location. Pharmacologic therapy produces the most favorable outcomes in distal ureteral stones, with proximal stones substantially less likely to pass spontaneously regardless of treatment.[9] MET demonstrates the greatest benefit for stones measuring 5–10 mm; smaller stones generally pass without pharmacologic assistance.[3]

Meta-analyses pooling data from multiple RCTs have reported stone expulsion rates of approximately 70–87% for alpha-blocker therapy versus 47–65% for placebo, representing a relative risk reduction in surgical intervention of approximately 40–57%.[7,8] Time to stone

expulsion is reduced by a mean of 3–6 days with alpha-blocker therapy compared to controls.[8]

4.2 Reduction in Colic, Analgesic Use, and Healthcare Utilization

In addition to improving expulsion rates, MET has been shown to significantly decrease the frequency and severity of renal colic episodes, reduce narcotic analgesic requirements, and decrease rates of hospitalization.[8] These effects collectively contribute to meaningful reductions in healthcare expenditure and avoidance of unnecessary surgical procedures.[2]

4.3 Adjunctive Role with Procedural Interventions

Alpha-adrenergic antagonists and calcium channel blockers may provide incremental benefit when used adjunctively in patients undergoing procedural interventions. Evidence suggests that MET administered following ESWL and ureteroscopy facilitates clearance of residual stone fragments, reduces post-procedural pain, and improves overall patient satisfaction.[11]

4.4 Safety and Tolerability

The safety profile of pharmacologic MET agents is generally favorable. Alpha-blockers are associated with dizziness, orthostatic hypotension, nasal congestion, and retrograde ejaculation; however, these adverse effects are typically mild and transient.[7] Calcium channel blockers may produce hypotension, headache, and peripheral edema, whereas corticosteroids carry metabolic and immunosuppressive risks when used over extended periods.[16] The favorable tolerability profile of alpha-blockers has solidified their status as the preferred first-line MET pharmacologic class.

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5. Conclusion

Medical expulsive therapy represents a highly effective, non-invasive treatment modality for appropriately selected patients with ureteral calculi—specifically those presenting with distal stones of approximately 10 mm or less who are suitable candidates for conservative observational management.[3,9] By relaxing ureteral smooth muscle, reducing spasms, and reducing intraluminal pressure, MET facilitates natural stone passage while maintaining patient comfort and avoiding procedural intervention.[13]

Alpha-adrenergic antagonists—particularly tamsulosin and silodosin—remain the pharmacologic cornerstone of MET, acting through inhibition of α1-adrenergic receptors in the distal ureter to reduce tone, peristaltic frequency, and intraluminal pressure.[7,14] Numerous RCTs and meta-analyses confirm that these agents substantially increase spontaneous expulsion rates, particularly for stones measuring 5–10 mm.[8]

Calcium channel blockers such as nifedipine offer an alternative mechanism via inhibition of L-type calcium channels in ureteral smooth muscle.[15] Early trials yielded promising results; however, the weight of current evidence positions them as second-line agents behind alpha-adrenergic antagonists in contemporary MET protocols.[5]

Despite robust evidence supporting MET, implementation in clinical practice remains suboptimal due to variability in physician awareness, inconsistent practice patterns, and conflicting results from large-scale trials.[10] Current AUA and EAU guidelines continue to support alpha-blocker use in appropriately selected patients with distal ureteral calculi, providing a clear evidence-based framework for

clinical decision-making.[3,4] Beyond standalone conservative management, alpha-blockers and calcium channel blockers provide adjunctive benefits in patients undergoing ESWL or ureteroscopy — facilitating fragment clearance, reducing post-procedural pain, and improving patient-reported outcomes.[11] Additionally, MET reduces analgesic requirements and symptomatic burden during the observation period, enhancing quality of life for patients awaiting spontaneous stone passage.[8]

In conclusion, MET represents a well-evidenced, cost-effective, first-line strategy for distal ureteral calculi amenable to conservative management. Adherence to evidence-based patient selection criteria and guideline-concordant prescribing practices will optimize stone passage outcomes, reduce patient morbidity, and decrease the rates of surgical intervention. Continued investigation into refined patient selection, optimal dosing, and combination regimens will further strengthen MET's role in contemporary urological practice.

References

[1] Türk C, Neisius A, Petrik A, et al. EAU Guidelines on Urolithiasis. European Association of Urology; 2022.

[2] Preminger GM, Tiselius HG, Assimos DG, et al. 2007 Guideline for the management of ureteral calculi. J Urol. 2007;178(6):2418–2434. doi:10.1016/j.juro.2007.09.107

[3] Pearle MS, Goldfarb DS, Assimos DG, et al. Medical management of kidney stones: AUA guideline. J Urol. 2014;192(2):316–324. doi:10.1016/j.juro.2014.05.006

[4] Assimos D, Krambeck A, Miller NL, et al. Surgical management of stones: AUA/Endourological Society guideline, part I. J Urol. 2016;196(4):1153–1160. doi:10.1016/j.juro.2016.05.090

ISBN 978-816855388-0

[5] Hollingsworth JM, Canales BK, Rogers MA, et al. Alpha blockers for treatment of ureteric stones: systematic review and meta-analysis. BMJ. 2016;355:i6112. doi:10.1136/bmj.i6112

[6] Pickard R, Starr K, MacLennan G, et al. Medical expulsive therapy in adults with ureteric colic: a multicentre, randomised, placebo-controlled trial. Lancet. 2015;386(9991):341–349. doi:10.1016/S0140-6736(15)60933-3

[7] Seitz C, Liatsikos E, Porpiglia F, Tiselius HG, Zwergel U. Medical therapy to facilitate the passage of stones: what is the evidence? Eur Urol. 2009;56(3):455–471. doi:10.1016/j.eururo.2009.06.012

[8] Campschroer T, Zhu X, Vernooij RW, Lock MT. Alpha-blockers as medical expulsive therapy for ureteral stones. Cochrane Database Syst Rev. 2018;4:CD008509. doi:10.1002/14651858.CD008509.pub3

[9] Miller OF, Kane CJ. Time to stone passage for observed ureteral calculi: a guide for patient education. J Urol. 1999;162(3 Pt 1):688–690. doi:10.1097/00005392-199909010-00014

[10] Furyk JS, Chu K, Banks C, et al. Distal ureteric stones and tamsulosin: a double-blind, placebo-controlled, randomized, multicenter trial. Ann Emerg Med. 2016;67(1):86–95. doi:10.1016/j.annemergmed.2015.06.001

[11] Bhatt NR, Davis NF, Flynn R, Thomas AZ, Manecksha RP, Thornhill JA. Dilemmas in the interpretation of evidence for the use of alpha-blockers in ureteric colic: a systematic review. BJU Int. 2019;124(5):740–750. doi:10.1111/bju.14777

[12] Scales CD Jr, Smith AC, Hanley JM, Saigal CS; Urologic Diseases in America Project. Prevalence of kidney stones in the United States. Eur Urol. 2012;62(1):160–165. doi:10.1016/j.eururo.2012.03.052

[13] Sigala S, Dellabella M, Milanese G, et al. Evidence for the presence of α1 adrenoceptor subtypes in the human ureter. Neurourol Urodyn. 2005;24(2):142–148. doi:10.1002/nau.20108