Intravesical aminophylline instillation as an alternative for balloon dilatation prior to semi-rigid ureteroscopic management of distal ureteral stones

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Abstract
Purpose In a randomized controlled trial, we evaluated the effect of intravesical aminophylline instillation (IVAI) on intravesical ureteral pressure of lower ureter and its use as an alternative to balloon dilatation after failure of advancing semi-rigid ureteroscope through the ureteric orifice without endodilatation.

Methods Our study included 83 patients with juxta-vesical distal ureteral calculi requiring endodilatation after unsuccessfully introducing the semi-rigid ureteroscope through the ureteric orifice. Patients were randomized into two groups: group A (study group) included 41 patients, where IVAI was used to dilate the ureter and facilitate ureteroscopy (the intravesical pressure was measured using a pressure transducer connected to an invasive pressure monitor before and 5 min after IVAI), whereas group B (control group) included 42 patients, where balloon dilatation was used prior to ureteroscopy. Perioperative surgical outcomes of ureteroscopy were evaluated in both groups.

Results A statistically significant decrease in mean intravesical ureteral pressure was found after IVAI from 12.34 ± 1.94 mmHg before injection to 8.46 ± 1.94 mmHg after injection (P < 0.001). Ureteral injuries, postoperative pain and hematuria were statistically significantly less among the study group compared to the control group (P < 0.05). We did not find statistically significant differences in operative time, need for DJ ureteral stenting or stone-free rate between both groups and no perioperative side effects were associated with IVAI.

Conclusion In ureteroscopic management of distal ureteral stones, intravesical aminophylline instillation is safe, inexpensive and effective in reducing intravesical pressure and achieves comparable outcomes to balloon dilatation with less ureteral injuries, postoperative pain and hematuria.

Keywords Ureteral stones · Distal ureteral stones · Aminophylline · Intraureteral pressure · Ureteroscopy · Balloon dilatation

Abbreviations
Atm Atmospheric
cAMP Cyclic adenosine monophosphate
cGMP Cyclic guanosine monophosphate
DJ Double J-stent
Fr French
IL-10 Interleukin 10
IVAI Intravesical aminophylline instillation
KUB X-ray for kidney, ureter and bladder
MET Medical expulsive therapy
NC-CTUT Non-contrast computer tomography for urinary tract
PDE Phosphodiesterase enzyme
RCT Randomized controlled trial
SD Standard deviation
SFR Stone free rate

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SPSS  Statistical package for social science
SWL  Shock wave lithotripsy

Introduction

Semi-rigid ureteroscopy is the treatment of choice for distal ureteric stones, being a cost-effective method with low morbidity, short hospital stay and high stone-free rate [1]. Ureteral dilatation prior to ureteroscopy is frequently required and should be simple, efficient and with minimal iatrogenic trauma [2]. Local intravesical aminophylline instillation (IVAI) was reported to facilitate ureteroscopy and tranureteral lithotripsy with reduced perioperative complications and increased stone-free rate [3].

We present the first clinical study to demonstrate the effect of IVAI on intraureteral pressure at the distal ureter and to evaluate its safety and efficacy as an alternative for balloon dilatation during ureteroscopy.

Patients and methods

During the period from October 2018 to October 2020, 365 patients with juxta-vesical lower ureteric stone ≤ 2 cm were evaluated. All patients were initially given medical expulsive therapy (MET) and tamsulosin and re-evaluated after 2 weeks. Patients with ureteric stones ≥ 10 mm on non-contrast computer tomography for urinary tract (NC-CTUT) and/or moderate to severe hydroureteronephrosis or severe pain were also given MET and tamsulosin and scheduled for prompt ureteroscopy. Comprehensive preoperative evaluation included medical and surgical history, complete physical examination, preoperative laboratory investigations and NC-CTUT.

We excluded patients with stones peeping at the ureteric orifice, having anatomic or functional renal disorders or any contraindication for aminophylline use; hypersensitivity to drug components, pregnancy or lactation (absolute contraindication); or presence of cardiologic, neurologic diseases, renal impairment or hepatic dysfunction (relative contraindication). Eighty-three patients were included in this randomized controlled trial (RCT) (Fig. 1).

In each case, direct semi-rigid ureteroscopy (using 8/9.5 fr. ureteroscope 27002L Karl Storz®, Germany) was initially attempted without endodilatation. On failure to advance the semi-rigid ureteroscope through the ureteric orifice, ureteroscopy was temporarily aborted and patients were randomly assigned to either IVAI followed by ureteroscopy (group A) or conventional ureteric balloon dilation before ureteroscopy (group B). Randomization was done through computer-generated list and sealed envelopes. In group A, intraureteral pressure was measured before and 5 min after IVAI.

All patients were operated under the same spinal anesthesia protocols and similar intravenous hydration. Patients were asked to fast overnight for 8 h and were given a third-generation cephalosporin as a prophylactic antibiotic at induction of anesthesia. Continuous intraoperative vital data, blood pressure, pulse and respiratory rate, were monitored by the attending anesthetologist to detect any possible systemic adverse effect of aminophylline.

Group A (study group) included 41 patients, who had their intraureteral pressure measured before and 5 min after intravesical instillation of 150 ml of the prepared solution (normal saline with aminophylline 250 mg/10 mL). The intraureteral pressure was measured using a pressure transducer connected to invasive pressure monitor by a 6-Fr double-lumen Amencath® urodynamic catheter introduced through the ureteric orifice distal to the ureteric stone. A safety guide wire was inserted prior to ureteroscopy without further ureteral dilatation. Group B (control group) included 42 patients; where a safety guide wire was initially inserted under fluoroscopy, dilatation of the lower ureter was achieved by Uromax™ balloon catheter at 20 atm for 2 min. Thereafter, a semi-rigid ureteroscope was introduced alongside the guide wire. Gentle trials to extract stones < 10 mm by stone forceps were performed initially. Failed gentle extraction of stones < 10 mm, stones ≥ 10 mm and/or impacted stones were fragmented with pneumatic lithotripsy before extraction. Holmium laser lithotripsy was spared for upper ureteric stones and flexible ureteroscopy (more cost-effective). At the end of the procedure, either a double J (DJ) stent or ureteric catheters were applied according to ureteral wall status and the presence of residual stones.

We evaluated stone-free rate (SFR), defined as no residual stones or insignificant residual fragments < 4 mm as found on postoperative NC-CTUT. All patients were monitored for pain after resolution of the effect of spinal anesthesia with visual analog scales every 4 h. Postoperative pain was evaluated through the need for analgesics in the first 24 postoperative hours. Postoperative complications, fever, hematuria, urinary tract infection and pyelonephritis, as well as postoperative aminophylline toxicity (tachycardia, arrhythmias, hypertension, seizures, restlessness, insomnia) were evaluated. We also assessed the need for postoperative extracorporeal shockwave lithotripsy (SWL) or re-do ureteroscopy.

Patients were followed up 3 months after discharge to assess 90-day postoperative complications through comprehensive history, focused clinical examination, urinanalysis, pelvi-abdominal ultrasonography and/or NC-CTUT as indicated.
**Statistical analysis**

Data were collected, coded and analyzed by the Statistical Package for Social Science (SPSS) version 23. Quantitative variables were presented as mean, standard deviations (± SD), while categorical variables were presented as numbers and percentages. The association of categorical variables was analyzed by Chi-square test and Fisher exact test (when the expected count in any cell was less than 5). The comparison between two independent groups with quantitative data and parametric distribution was done by independent *t* test. *P* value was considered significant if < 0.05 and highly significant if < 0.005.

**Results**

The mean age of patients included in our study was 38.1 ± 8.8 years. Fifty-eight patients (69.9%) were males. Nineteen patients (22.9%) had recurrent stone formation and 16 patients (19.3%) had previous ureteroscopy. Both groups were matched with no statistically significant differences in preoperative characteristics (Table 1).

Ureteral access was successful in all patients after IVAI in group A and after balloon dilatation in group B. There was a statistically significant (*P* < 0.001) decrease in intrarenal pressure after IVAI (8.46 mmHg ± 1.94) compared to pressure before injection (12.34 mmHg ± 1.94). Mean operative time was relatively longer, but not statistically significant in group A than in group B (*P* = 0.126). Gentle extraction of stones 5–9 mm without lithotripsy was successful in 62.5% (10/16) and 65% (13/20) in group A and group B, respectively. We found no statistically significant difference with regard to the need for lithotripsy between both groups (*P* = 0.406). Ureteral wall injuries were statistically significantly (*P* = 0.047) higher in group B (19%) compared to group A (4.9%). Balloon dilatation was associated with ureteral mucosal tear in 9.5%, submucosal false passage in 7.1% and ureteral perforation in 2.4% compared to ureteral mucosal tear in only 4.9% with IVAI. The need for intraoperative DJ stenting was not statistically significantly different between both groups (*P* = 0.335). No intraoperative
cardiovascular manifestations (tachycardia, arrhythmias or hypertension) or seizures from IVAI were observed (Table 2).

All patients were discharged 24 h after radiologic evaluation with NC-CTUT to assess SFR. Ureteric catheters were removed before discharge from hospital and DJ stents were removed after 2–3 weeks or after SWL if required.

Overall, SFR at first postoperative day was 88% (73/83). Stone-free rates were 87.8% (36/41) and 88.1% (37/42) in group A and group B, respectively, with no statistically significant difference in SFR between both groups (P = 0.968). Eight patients with residual stones underwent either SWL in 8.4% (7/83) or re-do ureteroscopy in 1.2% (1/83), whereas two patients with residual fragments 5–6 mm continued on medical treatment. Patients in group A had statistically significant less postoperative pain (P = 0.022) and required less analgesic (19.5% versus 42.9%). Postoperative hematuria was also statistically significant less in group A than in group B (P = 0.03). No postoperative IVAI associated toxicity was reported.

All patients were stone free at 3 months follow-up and we did not find statistically significant difference in 90-day postoperative urinary tract infection or pyelonephritis between both groups (Table 3).

### Table 1 Preoperative characteristics of patients included in our study

|                      | Group A (received aminophylline) (n = 41) | Group B (balloon dilatation) (n = 42) | Test value | P value |
|----------------------|------------------------------------------|--------------------------------------|------------|---------|
| **Age**              | Mean ± SD                                 | 37.83 ± 8.95                         | 38.36 ± 8.8 | 0.271   | 0.787   |
| **Sex**              | Male                                      | 30 (73.2%)                           | 28 (66.7%) | 0.417   | 0.518   |
|                      | Female                                    | 11 (26.8%)                           | 14 (33.3%) |          |         |
| **FH for urolithiasis** | No                                       | 29 (70.7%)                           | 33 (78.6%) | 0.675   | 0.411   |
|                      | Yes                                       | 12 (29.3%)                           | 9 (21.4%)  |          |         |
| **Stone recurrence** | No                                        | 32 (78%)                             | 32 (76.2%) | 0.041   | 0.84    |
|                      | Yes                                       | 9 (22%)                              | 10 (23.8%) |          |         |
| **Stone size**       | Mean ± SD                                 | 10.49 ± 3.23                         | 9.48 ± 3.51 | 1.367   | 0.176   |
| 1 – 4 mm             | 3 (7.3%)                                  | 6 (14.6%)                            |            |         |
| 5 – 9 mm             | 10 (24.4%)                                | 16 (39%)                             |            |         |
| 10 – 20 mm           | 22 (53.7%)                                | 18 (42.9%)                           |            |         |
| **Previous URS**     | No                                        | 31 (75.6%)                           | 36 (85.7%) | 1.361   | 0.243   |
|                      | Yes                                       | 10 (24.4%)                           | 6 (14.3%)  |          |         |

**FH** family history, **URS** ureteroscopy

### Table 2 Intraoperative evaluation

|                      | Group A (received aminophylline) (n = 41) | Group B (balloon dilatation) (n = 42) | Test value | P value |
|----------------------|------------------------------------------|--------------------------------------|------------|---------|
| **Operative time**   | Mean ± SD                                 | 38.1 ± 6.98                          | 35.64 ± 7.34 | 1.545   | 0.126   |
|                      | No                                       | 13 (31.7%)                           | 17 (40.5%)  | 0.691   | 0.406   |
| **Lithotripsy**      | Stone size 1-4 mm                        | 3 (7.3%)                             | 4 (9.5%)    |          |         |
|                      | 5-9 mm                                    | 10 (24.4%)                           | 13 (31%)    |          |         |
|                      | Yes                                       | 28 (68.3%)                           | 25 (59.5%)  |          |         |
| **Ureteral injury**  | Stone size 5–9 mm                        | 6 (14.6%)                            | 7 (16.7%)   |          |         |
|                      | 10-20 mm                                  | 22 (53.7%)                           | 18 (42.9%)  |          |         |
| **Stenting after ureteroscopy** | No                                      | 39 (95.1%)                           | 34 (81%)    | 3.931   | 0.047*  |
|                      | Yes                                       | 2 (4.9%)                             | 8 (19%)     |          |         |
| **Stent**            | Ureteral catheter                         | 33 (80.5%)                           | 30 (71.4%)  | 0.931   | 0.335   |
|                      | DJ stent                                  | 8 (19.5%)                            | 12 (28.6%)  |          |         |

SD standard deviation, DJ Double J

*Statistically significant
Discussion

Few studies evaluated upper tract pressure using different methods [4, 5]. Shafik used 3-Fr ureteric catheter to measure the ureteral pressure via a transducer output recorded on a rectilinear recorder [4]. Cai and colleagues measured the intraureteral pressure proximal to the stone after fragmentation during ureteroscopy via irrigation fluid through a ureteroscope connected to a pressure transducer recording the pressure on a pressure monitoring device [5]. The intraureteral pressures measured by Shafik [4] and Cai and colleagues [5] were 7.7 mmHg and 10.2 mmHg, respectively, were lower than the mean intraureteral pressure in our study (12.2±1.85 mmHg).

Several animal studies evaluated the effect of different medications on the modulation of ureteral contractions, peristalsis and smooth muscle relaxation of the upper urinary tract [6–8]. However in humans, only Jung and colleagues [9] demonstrated a statistically significant reduction in mean pelvic pressure using isoproterenol compared to saline instillation during flexible ureterorenoscopy.

Aminophylline is an inexpensive drug that has been widely available for decades. It is rapidly absorbed and converted to theophylline. The possible mechanism of action of theophylline is inhibition of phosphodiesterase enzyme (PDE), increasing the intracellular cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) levels leading to smooth muscle relaxation. Additional anti-inflammatory effects of theophylline are through adenosine receptor antagonism, inhibiting the release of inflammatory mediators, histamine, leukotrienes and superoxide anions, as well as stimulating the release of anti-inflammatory mediator interleukin 10 (IL-10) through inhibition of PDE. Theophylline also activates histone deacetylase downregulating the expression of inflammatory genes [10].

We demonstrated 3.88 mmHg mean reduction of intraureteral pressure at the distal ureter (12.34 mmHg and 8.46 mmHg before and after IVAI, respectively) and this decrease in ureteral pressure was associated with easy access through the ureteric orifice without endodilation, statistically significant less ureteric wall injuries, less hematuria and pain as well as comparable SFR.

The effect of local aminophylline instillation into the renal collecting system was studied by Green and colleagues, who demonstrated smooth muscle relaxation and facilitated intra-renal access to calyceal staghorn stones in ureteropelvic junction and/ or infundibular spasms [11].

A previous double-blinded RCT by Barzegarnezhad and colleagues [3] evaluated outcomes after IVAI compared to intravesical saline instillation in ureteroscopy for lower ureteric stones.

In our study, there was no statistically significant difference regarding SFR and operative time between cases which underwent IVAI or balloon dilatation; however, Barzegarnezhad and colleagues [3] demonstrated a statistically significantly higher SFR (95% versus 76.1% respectively) and

| Table 3 Postoperative outcomes |
|--------------------------------|
|                                 |
| **Group A** (received aminophylline) (n=41) | **Group B** (balloon dilatation) (n=42) |
| **Test value** | **P value** |
|----------------|------------|
| **SFR** | | |
| Free | 36 (87.8%) | 37 (88.1%) | 0.002 | 0.968 |
| Residual | 5 (12.2%) | 5 (11.9%) |
| **Pain** | | |
| No pain medication needed | 33 (80.5%) | 24 (57.1%) | 5.256 | 0.022* |
| Relieved by medication | 8 (19.5%) | 18 (42.9%) |
| **Hematuria** | | |
| No | 37 (90.2%) | 30 (71.4%) | 4.72 | 0.030 |
| Yes | 4 (9.8%) | 12 (28.6%) |
| **Management of residual stones** | | |
| SWL | 3 (66.7%) | 4 (100.0%) | – | 1.000 |
| Re-do URS | 1 (33.3%) | 0 (0.0%) |
| **90-days UTI** | | |
| Yes | 3 (7.3%) | 4 (9.5%) | – | 1.000 |
| No | 38 (92.7%) | 38 (91.5%) |
| **90-days Pyelonephritis** | | |
| Yes | 2 (4.9%) | 3 (7.1%) | – | 1.000 |
| No | 39 (95.1%) | 39 (92.9%) |

SFR stone free rate. SWL extracorporeal shock wave lithotripsy. URS ureteroscopy. UTI urinary tract infection

*Statistically significant
shorter duration for lithotripsy ($P = 0.01$) in favor of IVAI compared to saline instillation.

Barzegarnezhad and colleagues [3] also reported highly statistically significant reduction in both intraoperative need for DJ insertion and postoperative SWL ($P = 0.001$) with IVAI compared to saline instillation. Although our study demonstrated statistically significant less ureteral injuries ($P = 0.047$), we did not find statistically significant difference regarding the need for DJ insertion or the need for postoperative SWL between both groups ($P = 0.335$ and $P = 1$ respectively).

A major limitation for systemic use of aminophylline is its adverse effects. Nausea, vomiting and headache are associated with PDE4 inhibition, whereas palpitation and cardiac arrhythmias are associated with inhibition of PDE3. Neurologic stimulation, gastroesophageal reflux and diuresis are due to adenosine antagonism. Several drugs, diseases and diet may influence theophylline clearance through modulation of cytochrome P450 enzyme, e.g., ciprofloxacin, erythromycin, cimetidine and allopurinol, as well as hepatic diseases, pneumonia, renal impairment and congestive heart failure [10].

In concordance with the study of Barzegarnezhad and colleagues [3], we found no perioperative IVAI-related side effects.

Djaladat and colleagues [12] studied the effect of aminophylline on renal colic and reported that aminophylline can decrease renal pain and reduce the need for narcotics. Our study demonstrated statistically significant difference in both postoperative pain and hematuria after IVAI compared to balloon dilatation ($P = 0.04$ and $P = 0.03$, respectively).

A noticeable finding in our study was statistically significant reduction of ureteral wall injuries with IVAI compared to conventional balloon dilation. IVAI was also associated with less ureteral DJ stenting (19.5%) compared to balloon dilation (28.6%); however, this was not statistically significant.

To our knowledge, no previous clinical study evaluated the effect of IVAI on distal intraureteral pressure. Further studies should be encouraged to evaluate the best method for measuring intraureteral pressure and to study the effect of aminophylline and other pharmacologic agents to enhance the outcomes of ureteroscopic management of ureteric stones. The main limitation of our study is the small sample size. Large multicenter clinical trials are recommended to ascertain the use of IVAI as an alternative to balloon dilatation during extraction and lithotripsy of distal ureteric stones. Moreover, longer follow-up is needed to examine if the use of aminophylline solution for ureteral dilation (that causes minimal or no trauma to ureteral mucosa) instead of conventional balloon dilation may be associated with lower ureteric stricture rate or not.

**Conclusion**

Intravesical aminophylline instillation is safe, inexpensive and effective in reducing intraureteral pressure at the lower ureter and can be used as an alternative to balloon dilatation prior to ureteroscopic management of distal ureteric stones.

**Author contributions** All authors contributed to the design of the study, analysis of the results as well as drafting and revising of the manuscript.

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**Data availability** The datasets used and/or analyzed for the current study are available from the corresponding author on request.

**Declarations**

**Conflict of interest** There are no competing interests to declare.

**Ethical approval** Approval number: FMASU MS 116/2019.

**Consent for participate** Written informed consents were obtained from all patients before enrollement in the study.

**Consent for publications** All authors approved the final version of this manuscript and our manuscript has not been published previously or currently under consideration for publication elsewhere.

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**References**

1. AlSmadi JK, Li X, Zeng G (2019) Use of a modified ureteral access sheath in semi-rigid ureteroscopy to treat large upper ureteral stones is associated with high stone free rates. Asian J Urol 6:217–221
2. Özer C (2011) A simple technique for ureteral orifice dilatation in rigid ureterorenoscopy for distal ureteral stones. Can Urol Assoc J 5(6):E119–E120
3. Barzegarnezhad A, Firouzian A, Emadi SA, Mousanejad N, Bakhshali R (2012) The effects of local administration of aminophylline on transureteral lithotripsy. Adv Urol 2012:727843
4. Shafik A (1998) Ureteric profilometry: a study of the ureteric pressure profile in the normal and pathologic ureter. Scand J Urol Nephrol 32(1):14–19

5. Cai Y, Li X, Zhu B, Chen R, Ye C, Wang Y, Wang Y, Tao Y, Sun Q, Wen X (2012) A practical pressure measuring method for the upper urinary tract during uroscopy. Clin Invest Med 35(5):E322

6. Danuser H, Weiss R, Abel D, Walter B, Scholtyzik G, Mettler D, Studer UE (2001) Systemic and topical drug administration in the pig ureter: effect of phosphodiesterase inhibitors α1, β and β2-adrenergic receptor agonists and antagonists on the frequency and amplitude of ureteral contractions. J Urol 166(2):714–720

7. Stower MJ, Clark AG, Wright JW, Hardcastle JD (1986) The effect of various drugs on canine ureteric peristalsis. Urol Res 14(1):41–44

8. Bloch R, Decker N, Kostakopoulos A (1984) Effects of theophylline and isoproterenol on the activity on the isolated guinea pig ureter. Urol Int 39(5):308–311

9. Jung H, Nørby B, Frimodt-Møller PC, Oster P (2008) Endoluminal isoproterenol irrigation decreases renal pelvic pressure during flexible ureterorenoscopy: a clinical randomized, controlled study. Eur Urol 54(6):1404–1413

10. Barnes PJ (2010) Theophylline. Pharmaceuticals 3(3):725–747. https://doi.org/10.3390/ph3030725

11. Green DF, Glickman MG, Weiss RM (1987) Preliminary results with aminophylline as smooth-muscle relaxant in percutaneous renal surgery. J Endourology 1(4):243–247

12. Djaladat H, Tajik P, Fard SA, Alehashemi S (2007) The effect of aminophylline on renal colic: a randomized double-blind controlled trial. South Med J 100(11):1081–1084

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