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Effect of intraoperative aminophylline infusion on pain intensity after ureteroscopic lithotripsy: A randomized controlled study

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ABSTRACT

Background: Aminophylline relaxes smooth muscle by inhibiting the phosphodiesterase enzyme and activating protein kinase A, and alleviates inflammation by decreasing the production of leukotrienes. We aimed to assess the effect of intraoperative intravenous (IV) aminophylline on postoperative pain in patients undergoing ureteroscopic lithotripsy.

Methods: A randomized, placebo-controlled trial was conducted on 50 patients who were scheduled for ureteroscopic lithotripsy under general anesthesia. Patients were divided into two equal groups. Group 1 received 4 mg/kg aminophylline diluted in 100 ml saline 0.9% IV over 20 minutes. Group 2 received saline 0.9% with a similar volume and period as the aminophylline group. Visual analogue scale (VAS) score was recorded at arrival to the post-anesthesia care unit (PACU), 1 h, 2 h, 6 h, 12 h, and 24 h after surgery. Catheter-related bladder discomfort (CRBD) was assessed at PACU arrival, 1 h, 2 h, and 6 h postoperatively.

Results: VAS measurements at arrival to the PACU, 1 h, 2 h, and 6 h postoperative were significantly lower in group 1 than in group 2 ($p < 0.05$). Total pethidine consumption in the first 24 hours postoperatively was significantly lower in group 1 (43.04 ± 14.52 mg) than in group 2 (59.32 ± 18.34 mg); $p = 0.002$. Aminophylline significantly decreased the incidence of moderate-to-severe CRBD at PACU arrival and 1 h after surgery ($p = 0.005$ and 0.007, respectively). There was no significant variation between both groups regarding side effects.

Conclusions: In patients undergoing ureteroscopic lithotripsy, intraoperative IV aminophylline infusion reduced postoperative pain and opioid consumption. It also decreased the incidence of early moderate-to-severe CRBD without evidence of intraoperative hemodynamic alterations or postoperative side effects.

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1. Introduction

Ureteroscopy (URS) is a well-established, minimally invasive diagnostic and therapeutic method for upper urinary tract diseases. It is the most common upper urinary tract urolithiasis procedure [1].

URS frequently results in postoperative pain due to renal capsule distension and mechanoreceptor activation in the kidney and ureter [2]. Other possible pain mechanisms are ureteral spasms [3], and activation of chemoreceptors by mucosal irritation, ischemia, and inflammation [4,5]. In addition, the use of a ureteral access sheath has been linked to a rise in the production of the ureteral wall's inflammatory mediators, such as cyclooxygenase-2 (COX-2) and tumor necrosis factor-alpha (TNFα), which may contribute to higher postoperative pain [6].

Also, double-J (D-J) stent placement may be necessary to avoid complications in high-risk patients (residual stone fragments, ureteral edema or trauma, perforation, bleeding) [7]. It causes discomfort and contributes to postoperative pain due to the ureteral spasm associated with the D-J movement in the ureter [8,9].

Opioids play a major role in controlling postoperative pain. However, common adverse effects like sedation, nausea, vomiting, and respiratory depression limit its use as a sole agent. So, intraoperative multimodal analgesic protocols are preferred to establish adequate postoperative analgesia with minimal side effects [10].

Aminophylline, a methyl xanthine and theophylline derivative, relaxes smooth muscle by increasing the concentration of intracellular 3“,5”-cyclic adenosine monophosphate (cAMP), and cyclic guanosine monophosphate (cGMP) and activating protein kinase A. In addition, aminophylline alleviates inflammation by decreasing the production of leukotrienes and TNFα [11]. This spasmolytic, anti-inflammatory effect of aminophylline may have an analgesic role in surgeries like ureteroscopic lithotripsy. It was used in a previous study done by Djaladat [12] for managing acute renal

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colic due to ureteric stones. It was effective in producing analgesia and decreasing narcotic usage. Considering the similarity in the pathogenesis of pain between renal colic and URS [4,5,8,13], we assumed that aminophylline could provide analgesic effects in ureteroscopic surgeries.

So, we conducted this study to assess the effect of intraoperative intravenous (IV) aminophylline infusion on pain intensity after ureteroscopic lithotripsy. Our hypothesis was that aminophylline could decrease the postoperative visual analogue scale (VAS) pain scores together with a reduction in the doses of postoperative opioid and non-opioid medications.

2. Methods

This prospective randomized, placebo-controlled, double-blind study was conducted on 50 patients aged 18–50 years with American Society of Anesthesiologists (ASA) physical status ≤II, body mass index less than 30.0 kg/m^2, and ureteric stone scheduled for ureteroscopic lithotripsy with D-J ureteric stent placement at the end of the procedure under general anesthesia. The study was done at Tanta University Hospitals, Egypt, from February 2023 to June 2023. Enrollment of the patients was done after approval by the Institutional Ethical Committee of Tanta University (approval code 36264PR19/1/23) and registration in the clinical trials registry (ID: NCT05705050; https://clinicaltrials.gov/study/NCT05705050) by the primary investigator (OMR) on 30 January 2023. This article adheres to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. All participants signed written informed consent.

Exclusion criteria were central nervous system diseases, cardiovascular diseases, arrhythmias, cerebrovascular diseases, convulsions, renal or hepatic impairment, pregnancy or lactation, history of allergy to aminophylline, excessive coffee intake (greater than two cups each day), opioid-dependent individuals and those on B-agonists, antidepressants, or tranquilizers, and short procedures (less than 30 minutes).

Patients were assigned randomly in a parallel manner into two equal groups, utilizing computer-generated numbers and sealed opaque envelopes. Patients in the aminophylline group (Group 1) received 4 mg/kg aminophylline (Etaphylline™, Memphis for Pharmaceutical & Chemical Industries, Egypt) diluted in 100 ml saline 0.9% IV over 20 minutes after anesthesia induction and positioning in the lithotomy position. Patients in the saline group (Group 2) were given an equivalent volume of isotonic saline throughout the same duration. A nurse anesthetist (not involved in our study) prepared the study solutions. A single anesthesiologist performed standardized anesthetic management, including the administration of the study solutions, which were prepared in identical syringes and volumes. The study drugs were given over a period of 20 minutes to avoid any hemodynamic changes that may occur with the rapid IV injection of aminophylline, which could affect its blinding. A single surgeon performed all procedures, and a second anesthesiologist collected the intraoperative data and assessed the postoperative outcomes. Patients, anaesthesiologists, and the surgeon were all blinded to group allocation.

Non-invasive arterial pressure, pulse oximetry, ECG, temperature probe, and capnogram were used for intraoperative monitoring. 1.5 µg/kg fentanyl, 2 mg/kg propofol, and 0.5 mg/kg atracurium were used for anesthetic induction. The end-tidal carbon dioxide concentration was kept between 35 and 40 mmHg by adjusting the ventilation settings. Sevoflurane [one minimum alveolar concentration (MAC)] in air/oxygen was used to sustain anesthesia. The study solutions were given after positioning the patients in the lithotomy position at the start of the ureteroscopic procedure. Top-up doses of 0.1 mg/kg atracurium were given to maintain the neuromuscular block when needed. An intraoperative acetaminophen (15 mg/kg) IV infusion was given to all patients.

Mean arterial blood pressure (MAP) and heart rate (HR) were recorded before induction (baseline), after intubation, every 10 minutes intraoperatively, and after extubation. Intraoperative hypertension or tachycardia (MAP and HR values exceeded 20% of baseline) was treated by increasing the anesthesia depth by increasing the inhalational anesthetic concentration to 1.3 of MAC and administering intravenous 50 µg fentanyl. Hypotension was treated by decreasing the inhaled anesthetic concentration to 0.7 of MAC and giving 5 mg ephedrine. If HR decreased < 50 beats/min, an IV bolus of 0.5 mg atropine was applied.

At the surgery end, the ureter was stented using a 6F D J, and the patients were catheterized (for a minimum duration of 12 hours) with a 16F Foley catheter, and 10 ml saline (0.9%) was used to inflate the balloon. The neuromuscular block was reversed by neostigmine and atropine. Extubation was done after fulfilling the extubation criteria. Then, patients were transferred to the post-anesthesia care unit (PACU). 15 mg/kg acetaminophen IV was given every 8 hours for postoperative analgesia (the first dose was given 6 hours after surgery). Postoperative pain was assessed using a 10 cm VAS pain score; 0= no pain to 10= worst pain) at arrival to the PACU, 1 h, 2 h, 6 h, 12 h, and 24 h after surgery. VAS score ≥ 4 was managed by 0.5 mg/kg pethidine IV. The time to first pethidine requirement and the total pethidine dose on the first postoperative day were recorded. Catheter-related bladder discomfort (CRBD), manifested as the need to pass urine or suprapubic region discomfort [14], was assessed (when assessing VAS) at PACU arrival, 1 h, 2 h,

and 6 h postoperatively. Severity of CRBD was graded as mild (reported only if the case asked about it), moderate (reported spontaneously and without any action responses), or severe (reported spontaneously and with action responses in the form of a tough vocal response or efforts to remove the catheter [15].

Patients with moderate or severe CRBD were given 30 mg ketorolac IV infusion (a second dose could be given within the 1st 12 hours after surgery). The number of patients who required ketorolac and the total ketorolac dose in the first 12 hours postoperatively were assessed. Before surgery, all cases were taught how to use a VAS to rate their pain and were instructed about the symptoms of CRBD.

Our primary outcome was VAS at arrival to the PACU. The secondary outcomes were VAS values after discharge from PACU (at 1, 2, 6, 12, and 24 hours after surgery), time to 1st opioid requirement, total pethidine dose on the 1st day after surgery, incidence of moderate-to-severe CRBD (at PACU arrival, 1 h, 2 h, and 6 h postoperative), number of patients required ketorolac and the total ketorolac dose in the first 12 hours postoperative, and the incidence of adverse reactions.

2.1. Sample size justification

G*Power 3.1.9.2 (Universitat Kiel, Germany) performed the sample size estimation. Based on our pilot study (10 cases in each group), the mean (± SD) VAS score in PACU was 2.8 ± 1.23 in Group 1 and 3.9 ± 1.2 in Group 2. This yielded a 0.905 effect size. With a two-tailed t test, 95% confidence limit, and 80% power of the study, 21 patients were required for each group. To compensate for dropouts, a total of 50 patients were recruited.

2.2. Statistical analysis

SPSS v27 (IBM, Armonk, NY, USA) was used to analyze the data. Histograms and the Shapiro-Wilks test analyzed the data distribution normality. Unpaired student t-tests analyzed quantitative parametric data expressed as mean ± SD (VAS scores, time to first pethidine request, total pethidine consumption in the first postoperative day, and the total ketorolac dose in the first 12 hours after surgery). Qualitative variables expressed as frequency (%) (CRBD incidence, number of cases who required ketorolac or experienced postoperative side effects) were analyzed by chi-square or Fisher's exact test as appropriate. p value < 0.05 indicated significance.

3. Results

In this study, the eligibility of 68 patients was evaluated; 11 patients were not eligible, and 7 declined to participate in the trial. The rest of the patients were randomized into two groups (25 patients each). Five patients were excluded from statistical analysis as one patient had a surgical duration of less than 30 minutes, and four patients did not require a DJ stent. Therefore, 23 patients in group 1 and 22 patients in group 2 were analyzed (Figure 1).

Demographic data, duration of surgery, and stone location were comparable between groups (Table 1).

VAS measurements at PACU arrival, 1 h, 2 h, and 6 h were significantly lower in group 1 than in group 2 (p value < 0.05) and were insignificantly different at 12 h and 24 h between both groups (Table 2).

Intraoperative HR and MAP measurements at baseline, after intubation, 10 min, 20 min, 30 min, 40 min, 50 min, 60 min, and after extubation varied insignificantly between groups (Figure 2).

Group 1 had a significantly lower overall incidence of CRBD at PACU arrival and at 1 hour after surgery compared to group 2 [at PACU: 26% vs 59%; p value = 0.025; and at 1 hour: 30.4% vs 72.7%; p value = 0.005]. Also, the incidence of moderate-to-severe CRBD was significantly lower in group 1 compared with group 2 at PACU arrival and at 1 h postoperatively (at PACU: 8.7% vs 45.45%; p value = 0.005; and at 1 h: 4.3% vs 36.36%; p value = 0.007). It did not differ significantly between both groups at 2 h and 6 h post-surgery (Table 3).

Only one patient in each group required intraoperative supplementation with a single 50 µg fentanyl IV dose. The time to first rescue analgesia was significantly delayed in group 1 compared to group 2 (2.67 ± 2.4 h vs 1.02 ± 0.99 h; p value = 0.005). Total pethidine consumption was significantly lower in group 1 than in group 2 (43.04 ± 14.52 mg vs 59.32 ± 18.34 mg; p value = 0.002). The number of patients who required postoperative ketorolac was significantly lower in group 1 as compared to group 2 (p value = 0.017). The total ketorolac dose in the first 12 hours postoperatively was significantly lower in group 1 than in group 2 (p value = 0.024) (Table 4).

Intraoperative complications (hypotension, arrhythmia, and bradycardia) and post-operative side effects [postoperative nausea and vomiting (PONV), headache, shivering, and lightheadedness] were non-significantly different between both groups. Only one patient in group 2 developed bradycardia. The incidence of hypotension was two patients (8.7%) in group 1 versus one patient in group 2 (4.55%). None of our patients experienced arrhythmia. PONV occurred in three patients in group 1 and in two patients in group 2. In group 1, one case experienced headache, one shivered, and one felt lightheadedness.

4. Discussion

Our trial revealed three key findings. First, intraoperative IV aminophylline led to a significant decrease in the 1st 6 hours postoperative VAS and

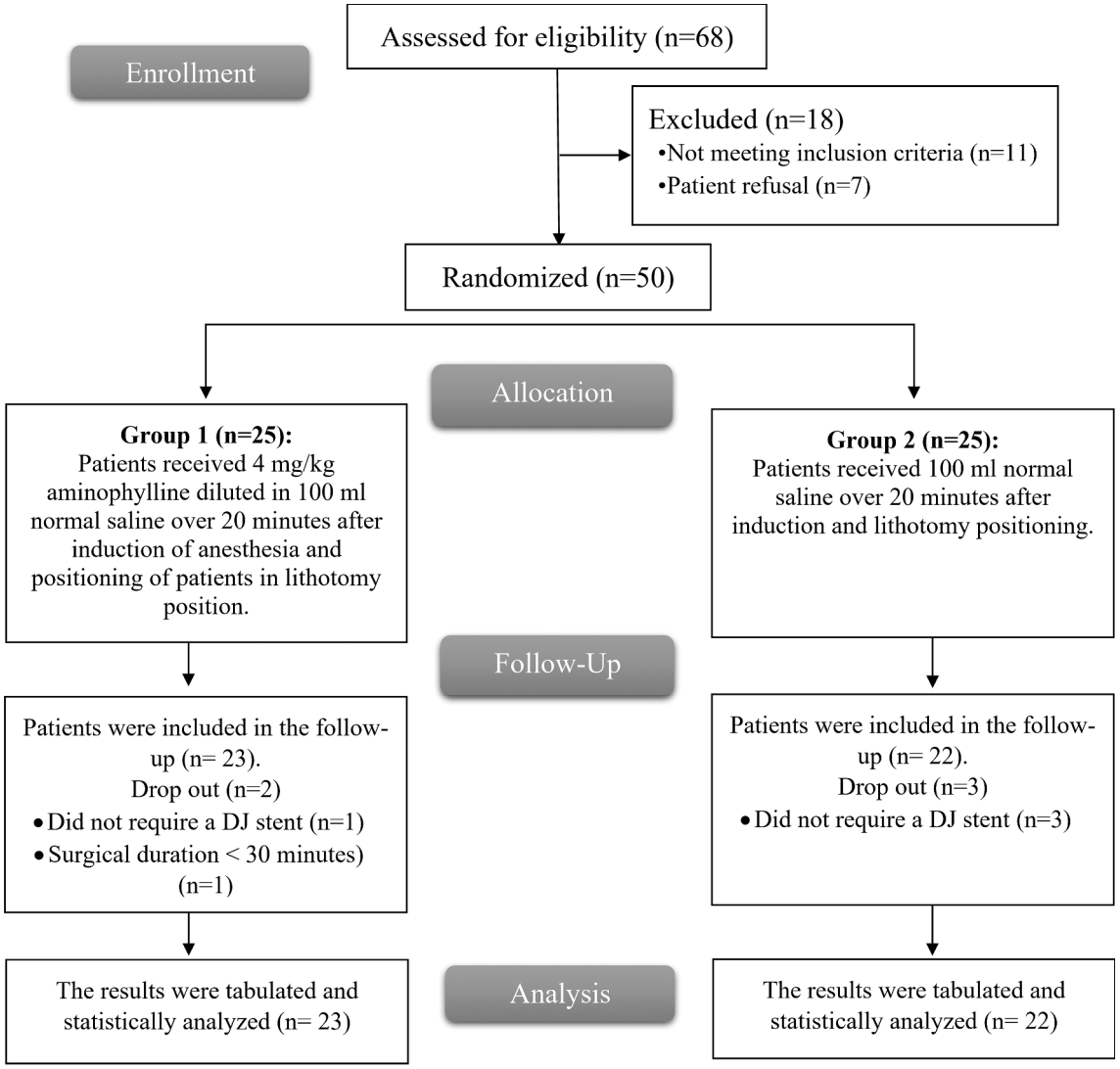


Figure 1. CONSORT flowchart of the enrolled patients.

Table 1. Demographic data, duration of surgery and stone location of the studied groups.

		Group 1 ($n = 23$)	Group 2 ($n = 22$)	P value
Age (years)		40.78 ± 6.27	39.14 ± 6.79	0.402
Sex	Male	14 (60.87%)	16 (72.73%)	0.399
	Female	9 (39.13%)	6 (27.27%)	
Weight (kg)		71.48 ± 7.77	73.18 ± 6.54	0.431
Height (m)		1.66 ± 0.06	1.63 ± 0.06	0.071
BMI (kg/m^2)		25.85 ± 2.8	27.72 ± 3.91	0.072
Stone location	Upper third ureter	9 (39.13%)	8 (36.36%)	0.893
	Middle third	4 (17.39%)	4 (18.18%)	
	Lower third	2 (8.69%)	2 (9.09%)	
	Multiple	4 (17.39%)	6 (27.27%)	
	Pelvi-ureteric junction	4 (17.39%)	2 (9.09%)	
Duration of surgery (min)		71.96 ± 11.75	75.68 ± 9.42	0.248

Data are presented as mean ± SD or frequency (%), BMI: Body mass index.

a significant decrease in the rescue pethidine dose required on the 1st postoperative day. Second, the incidence of early moderate-to-severe CRBD (up to 1 hour postoperatively) and the total ketorolac dose in the first 12 hours postoperatively were significantly decreased in the aminophylline group. Third, there was no evidence of significant intraoperative hemodynamic alteration or postoperative side effects.

URS procedures can be done under local or spinal anesthesia in selected cases. However, general anesthesia is usually required [16]. The rationale may be to regulate tidal volume to prevent excess unwanted diaphragmatic, renal, and ureteric movements, which cause unstable access to stones, mucosal ureteric injury, and an unsmooth surgical procedure [17,18].

Pain after ureteroscopic procedures can be attributed to the renal collecting system, renal capsule, and

Table 2. Visual analog scale (VAS) of the studied groups.

	Group 1 ($n = 23$)	Group 2 ($n = 22$)	P value
At arrival to PACU	2.39 ± 1.37	3.77 ± 1.88	**0.007***
1 h	2.57 ± 1.41	3.68 ± 1.65	**0.017***
2 h	2.39 ± 1.34	3.59 ± 1.56	**0.008***
6 h	1.83 ± 0.94	2.55 ± 0.67	**0.005***
12 h	1.13 ± 0.46	1.41 ± 0.5	0.058
24 h	0.78 ± 0.6	1 ± 0.53	0.207

Data are presented as mean ± SD. PACU: Post-anesthesia care unit, *: Significant when $p \leq 0.05$.

Table 3. Bladder discomfort of the studied groups.

	Group 1 ($n = 23$)	Group 2 ($n = 22$)	P value
Incidence of discomfort			
At arrival to PACU	6 (26%)	13 (59%)	**0.025***
1 h	7 (30.4%)	16 (72.7%)	**0.005***
2 h	7 (30.4%)	11 (50%)	0.181
6 h	10 (43.4%)	7 (31.8%)	0.420
Incidence of moderate-to-severe discomfort			
At arrival to PACU	2 (8.7%)	10 (45.45%)	**0.005***
1 h	1 (4.3%)	8 (36.36%)	**0.007***
2 h	2(8.7%)	5 (22.73%)	0.243
6 h	5 (21.74%)	2 (9.09%)	0.414

Data are presented as frequency (%). The chi-square was used to compare group 1 to group 2. *: Significant when $p \leq 0.05$, PACU: Post-anesthesia care unit.

ureter distention, leading to stimulation of the nociceptors and reflex muscle spasm [19]. After URS, DJ stent placement is also considered a predictor for acute postoperative pain [20,21]. Aminophylline (a combination of theophylline and ethylenediamine) is a cheap medication that has been accessible for a long time. The possible mechanism of action is adenosine receptor antagonism, raising the levels of cAMP and cGMP inside the cells, and enhancing K^+ efflux. Moreover, aminophylline leads to the relaxation of smooth muscles due to a decrease in Ca^{++} influx-associated contractility. Theophylline also inhibits the release of mast cells' adenosine-induced mediators, TNF-α, and superoxide anion [22]. These effects could be responsible for the analgesic profile encountered in our study.

Previous studies addressed the role of aminophylline in accelerating the recovery of patients from anesthesia depending on its central adenosine receptor antagonism property [23–26], and some studies used aminophylline to manage postdural puncture headache [27]. However, no previous studies have assessed the analgesic efficacy of IV aminophylline in urologic procedures.

A recent study [28] evaluated the effect of 4 mg/kg aminophylline (IV over 10 minutes) before the end of deep vitrectomy surgery, and its results reported that the pain score was significantly lower in the aminophylline group than in the placebo group for the first four hours postoperative.

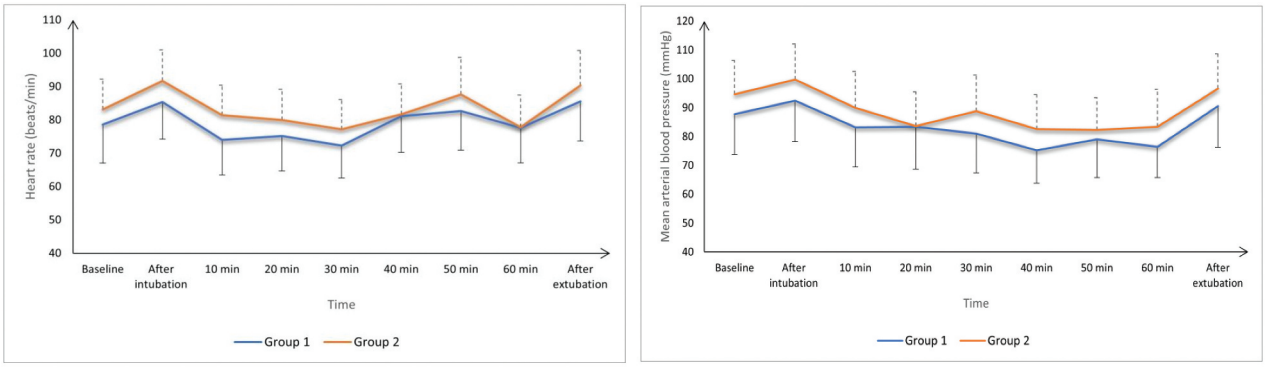
Also, El Tahan et al. [25] administered various dosages of aminophylline (2, 3, 4, or 5 mg/kg) or saline at the end of anesthesia to patients scheduled for different types of surgeries. They revealed that the pain scores after extubation and at PACU arrival were significantly lower in the aminophylline groups than in the saline group.

Shabayek et al. [29] found a significant reduction in the intraureteral pressure with local aminophylline administration (intravesical instillation of 150 ml saline

Table 4. Number of patients required intraoperative fentanyl and postoperative analgesic profile in both groups.

	Group 1 ($n = 23$)	Group 2 ($n = 22$)	P value
Number of patients required intraoperative fentanyl	1 (4.35%)	1 (4.55%)	1
Time to first rescue analgesia (h)	2.67 ± 2.4	1.02 ± 0.99	**0.005***
Total pethidine consumption in the 1st day (mg)	43.04 ± 14.52	59.32 ± 18.34	**0.002***
Number of patients required ketorolac	9 (39.13%)	17 (77.27%)	**0.017***
Total ketorolac dose in the 1st 12 hours after surgery	30 ± 0	42.35 ± 15.22	**0.024***

Data are presented as mean ± SD or frequency (%),*: Significant when $p \leq .05$.



(A) (B)

Figure 2. Intraoperative heart rate (A) and mean arterial blood pressure (B) of the studied groups.

solution containing 250 mg aminophylline) in 41 patients before URS. This ureteric smooth muscle relaxant effect resulted in less postoperative pain and less analgesic requirements in these patients. Also, Djaladat [12] and his colleagues assessed the role of 6 mg/kg aminophylline infusion over 30 minutes on renal stone-induced colic. This provided superior analgesia, as demonstrated by a significant reduction in VAS scores with aminophylline compared to placebo at 30 and 60 minutes after infusion.

In our study, aminophylline significantly decreased VAS score values in the first 6 hours after surgery. The elimination half-life of aminophylline in adults is 8–9 hours [30], and this clearance rate could explain the non-significant difference in VAS scores between both groups at 12 hours and 24 hours after surgery.

Regarding CRBD, aminophylline significantly decreased the incidence of moderate-to-severe CRBD at PACU arrival and 1 hour after surgery. The activation of muscarinic receptors or inflammation-induced smooth muscle contractions in the urinary bladder is responsible for CRBD manifestations [31]. Since the urinary bladder is part of the urinary tract, aminophylline's anti-inflammatory and smooth muscle relaxant properties may have alleviated CRBD manifestations. Although the significant value of aminophylline regarding this issue was limited to only one hour after surgery, the ketorolac dose required in the first 12 hours postoperatively for moderate-to-severe CRBD was significantly decreased in the aminophylline group. The non-significant difference in the incidence and severity of CRBD between both groups after 1 hour postoperative may be attributed to the earlier pethidine administration in group 2 (1.02 ± 0.99 h). Pethidine is known to have anticholinergic effects due to its structure similarity to atropine [32]. Anticholinergic drugs block the muscarinic receptors in the urinary bladder and were considered to be a viable method for CRBD control [33].

Regarding aminophylline-related side effects, our results demonstrated that aminophylline didn't produce significant changes in the intraoperative hemodynamics, and no significant postoperative side effects were detected. This is consistent with Hüpfl et al. [24] who found that the effects of aminophylline (3 mg/kg IV over 1 minute) on HR and MAP were similar to placebo (saline). Tachycardia, arrhythmia, and other adverse effects were not experienced by any patient in their study.

Also, El Tahan et al.'s [25] results revealed that the four aminophylline groups did not differ significantly from the placebo group regarding perioperative HR, MAP, arrhythmia, tremors, nausea, and vomiting.

Moreover, Kasim and his colleagues [26] revealed that injecting aminophylline at doses of 2 mg/kg and 4 mg/kg over 10 minutes didn't produce a significant difference in the intraoperative HR or MAP values between the aminophylline groups and the saline group, with no reported side effects related to aminophylline administration.

Djaladat et al. [12] found that a non-significant proportion (only 7.1%) of patients who received 6 mg/kg aminophylline for renal colic reported self-limited headache and dizziness.

Contrary to our results, Turan et al. [23] reported that HR significantly increased in patients who received IV aminophylline (5 mg/kg) compared to those who received saline at the end of surgery. This increase in HR can be explained by the higher dose of aminophylline used and the timing of its administration after inhalational anesthetic closure, which makes patient recovery a cofactor in producing tachycardia.

Also, Ghaffaripour et al. [34] found that IV injection of aminophylline at a dose of 4 mg/kg resulted in a significant increase in HR and MAP values compared to saline injection. Although the aminophylline dose given was similar to our study, a shorter duration of injection (2 minutes) and timing of administration at patient recovery could explain the difference. Aminophylline must be given very slowly over at least 20 minutes to avoid its harmful effects on the cardiovascular system and the central nervous system [30].

4.1. Limitations

First, we didn't assess the serum aminophylline concentration. Second, although the total pethidine and ketorolac doses were statistically significantly decreased in the aminophylline group, the difference between both groups may be of little clinical benefit. To increase the clinical benefits, a larger aminophylline dose (up to 5.4 mg/kg) or a second dose on the first postoperative day may be considered. Third, this study was conducted only on patients who required DJ stent placement after URS, and the analgesic benefits of aminophylline in other urologic procedures need to be evaluated.

5. Conclusion

In patients undergoing ureteroscopic lithotripsy, an intraoperative IV aminophylline infusion decreased pain and opioid use after surgery. It also decreased the incidence of early moderate-to-severe CRBD and ketorolac needs, without evidence of intraoperative hemodynamic alterations or postoperative side effects.

Disclosure statement

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Author contribution

Osama Mohammed Rehab, this author helped study concept and design, acquisition and interpretation of data, drafting the manuscript, revising it and approved the final version.

Mohammed Said ElSharkawy, this author helped analyze the study data, generate figures, revising, editing the manuscript, and approved the final manuscript.

Abdullah Salah Al Debeiky, this author helped design of the work, performed the review of the manuscript, and read and approve the final manuscript.

Islam Morsy; this author helped study design, interpretation of data, revising manuscript critically for important intellectual content, and approved the final manuscript.

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