

# A Comparison Study between Theophylline and Placebo in Passage of Ureteral Stones

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## ABSTRACT

**Purpose:** Considering the high prevalence of urinary system stones and that non-medical treatments have more costs and side effects, we decided to evaluate the effect of theophylline in the passage of ureteral stones.

**Materials and Methods:** One hundred and fifty patients with ureteral stones were assigned into groups A and B, whose age, sex, size of stone, and location of stone were matched together. Patients' ages ranged from 17 to 67 years. In group A theophylline (200 mg BID) was administered and group B received placebo for six weeks. Both groups were followed up by visits every fortnight and radiological assessment was performed at the end of the sixth week. The proportion of patients whose stones were passed was compared between the two groups.

**Result:** In group A with theophylline consumption 46 out of 75 (61.3%) passed their stones. The mean duration between the initiation of the treatment with theophylline and stone passage was 18.3 days. In group B with placebo, the stone passage occurred in 31 out of 75 (41.3%) patients ( $p < 0.032$ ) and the mean duration was 24.8 days ( $p < 0.05$ ).

**Conclusion:** With regard to the findings of this study, it seems that theophylline can increase the rate of ureteral stone passage and as well, accelerate it.

**KEY WORDS:** Theophylline, urolithiasis, stone passage

## Introduction

Ureteral stones substantially originate from kidney and then are released into ureter. Entrapment of the stone in the ureter and subsequently initiating the symptoms occurs when the stone is greater than 2 mm. Factors associated with spontaneous passage of stones consist of size and shape of stone, anatomical narrowing in ureter, ureteral peristalsis, hydrostatic pressure of urine over the stone, edema, and inflammation and spasm of ureteral wall in the stone location. From the above, hydrostatic pressure of urine and relaxation of ureter in the stone location, have a great importance.<sup>(1)</sup>

As concerns the great effect of ureteral relaxation in the stone location and considering that theophylline can relax the smooth muscles of ureteral wall by increasing cAMP, it comes into question whether theophylline have a positive

effect on the passage of ureteral stones or not and if the answer is yes, how much the amount of this effect is. Accordingly, we intended to design this study in order to evaluate the effect of theophylline on the ureteral stone passage.

## Materials and Methods

In this prospective clinical trial, 150 patients with ureteral stone, who had been presented to the urology clinic of Noor hospital and did not have the indication of surgical management, were selected. Diagnosis of urolithiasis had been confirmed by KUB and ultrasonography or IVP.

The range of the patients' ages was 17 to 67 years and they were 105 males and 45 females. The stones size varied from 3 mm to 9 mm. The patients were assigned into two groups each contained 75 persons. In order to decrease the confounding factors, the two groups were matched according to gender, age, stone location, and

stone size (table 1). Matching was done trying to provide identical distributions of gender and age, and minimizing the differences in the size and location of stones.

Stratified randomization was performed according to the location of the stone and gender.

theophylline (200mg/BD) was prescribed for group A, including 23 female and 52 male and placebo (capsules containing sugar) for group B, including 22 female and 53 male. Neither the patients nor the data collectors were aware of the kind of prescribed capsules. The analgesic used for pain was the same in both groups. The patients were recommended to control the passage of stone in their urine. The patients' informed consent had been taken by completely instructing the study.

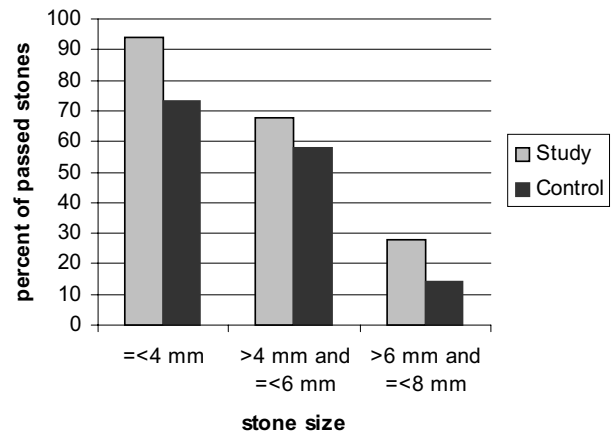
Both groups were followed up by every fortnight visits and radiological assessment was performed at the end of the sixth week. The groups were compared with each other according to the passage of the stone and the duration of the passage from the beginning of the treatment. For statistical analysis proportional competence exam was used.

## Results

In group A, 46 out of 75 patients who received theophylline, passed their stones (61.3%); whereas, in group B (placebo), ureteral stone passage occurred in 31 cases (41.3%) ( $p < 0.032$ ). As figure 1 shows, greater proportions of smaller stones were passed in both groups. However, theophylline effect in increasing the percent of stones passed is recognizable in all stone size groups; with regard that the percent of stones 4 mm or smaller, which were passed, was 73% in group B and 94% in group A. In cases with stones

**TABLE 1.** Characteristics of stone size and location in study (A) and control (B) groups.

Ureteral Stones	Study (A) group No.(%)	Control (B) group No.(%)
<b>Size of the stone</b>		
≤4 mm	16 (21.3)	15 (20)
>4 mm and ≤6 mm	38 (50.6)	38 (50.6)
>6 mm and ≤8 mm	14 (18.6)	14 (18.6)
>8 mm and ≤9 mm	7 (9.3)	8 (10.6)
<b>Location of stone</b>		
Upper	7 (9.3)	8 (10.6)
Middle	17 (22.6)	16 (21.3)
Lower	51 (68)	51 (68)
Total	75 (100)	75 (100)



**FIG. 1.** The rate of passed stones in each group according to the size of the stone

between 4 mm and 6 mm, the percent of the passed stones was 58% in group B and 68% in group A. Eventually 14% of the stones 6 to 8 mm in diameter were passed in group B, whereas this percent was 28% in group A (table 2).

In this study, age and gender did not influenced theophylline effect on stone passage. Mean duration from the beginning of treatment to stone passage was 24.8 (range 4 to 41) days in group B and 18.3 (range 2 to 33) days in group A ( $p < 0.05$ ).

**TABLE 2.** Number of passed stones in study and control groups according to the size of stones.

Size of the stone	Study (A) group No.(%)	Control (B) group No.(%)
≤4 mm	15 (94)	11 (73)
>4 mm and ≤6 mm	26 (68)	18 (58)
>6 mm and ≤8 mm	4 (28)	2 (14)
>8 mm and ≤9 mm	1 (14)	0 (0)

## Discussion

Several factors are associated with ureteral stone passage, of which the most important is stone diameter. In one study it has shown that the probability of spontaneously stone passage in stones smaller than 4 mm, 4 to 6 mm, and larger than 6 mm in diameter are 80%, 59%, and 21%, respectively.<sup>(2,3)</sup> Furthermore, the rate of spontaneous passage largely depends on the stone location. This rate in upper, mid, and lower ureter was 22%, 46%, and 71%, respectively, attained in a study by Morse and colleagues.<sup>(4)</sup>

Also, Miller et al<sup>(5)</sup> demonstrated that being smaller and more distal in ureter was associated with higher probability of stone passage as well as being in the right ureter; however, age, sex, and intensity of pain had no effect. In this study

in 1999, it was observed that ample treatment period for the stones, 2 mm or smaller in size, was 31 days, and for the stones 2 to 6 mm was 40 days.

In our study, the average duration from the beginning to the end of passage was 18.3 days in group A and 24.8 days in group B.

There are different methods in treatment of urinary stones. In a research on 180 patients with urinary stones, performed in the United States, they showed a tendency towards medical treatment, specially in the ones who had undergone interventional procedures such as surgery, ESWL, etc.<sup>(6)</sup>

Concerning the effects of different medical agents on ureter, it has been observed that although ureteral smooth muscles relaxation may be independent on cyclic nucleotides, it is believed that cyclic adenosine monophosphate (cAMP) has a mediatory role in ureteral relaxation depending on  $\beta$ -adrenergic agonists in smooth muscles.<sup>(1)</sup>

In a research in 2001, it was seen that isoproterenol sulfate, as a  $\beta$ -agonist adrenoreceptor, largely decreased the friction between artificial stone and ureteral wall in rabbits and it was strongly suggested that loosening of smooth muscles by means of  $\beta$ -adrenergics can decrease the ureteral wall tension as the mechanical inhibitory effect of stone movement.<sup>(7)</sup> In another study, it was demonstrated that the inhibitory effect of prostaglandin E1 on the function of ureter in hamsters is along with increasing the level of cAMP.<sup>(8)</sup>

Moreover, it was seen that the inhibitors of phosphodiesterase enzyme such as theophylline and papaverine can increase the level of intracellular cAMP and subsequently, relax ureteral smooth muscles.<sup>(1)</sup>

Theophylline is an agent that directly relaxes the smooth muscles in bronchi and vessels, and so does in ureter. This effect seems to be largely associated with increasing cAMP. The other suggested mechanisms for theophylline effect are: changing the concentration of calcium ion in smooth muscles, inhibiting the prostaglandin effects on smooth muscles, blocking adenosine receptors, and inhibiting of histamine and leukotrienes release from mastocytes. Theophylline also has other effects such as dilation of coronary arteries, increasing the urine output, and stimulation of brain, heart and skeletal muscles. It is highly absorbed orally. It metab-

olizes in liver through which it is converted into caffeine. Theophylline is removed by kidneys, almost 10% of which is detectable unchanged in urine.<sup>(9)</sup>

In a study by Becker et al, the effect of theophylline on ureteral peristalsis was investigated. They concluded that it can be used in renal colic and hence, it can ease the passage of ureteral stones.<sup>(10)</sup> In another study, it was shown that invitro relaxing of rabbit ureter by theophylline facilitates the stone passage.<sup>(11)</sup>

Referring to authentic databases, it is seen that the other researches are in process, such as the one by Audsoo and Asuanc in Yale urology department.

## Conclusion

Due to theophylline's effect on relaxing of ureteral smooth muscles, and the relaxation of the ureter in stone site, the administration of the drug in selected patients with ureteral stone will facilitate the ureteral stone passage.

## References

1. Weiss RM. Physiology and pharmacology of the renal pelvis and ureter. In: Walsh PC, Retik AB, Vaughan ED Jr, Wein AJ, editors. Campbell's Urology. 8<sup>th</sup> ed. Philadelphia: WB Saunders; 2002. p. 377-403.
2. Stoller ML, Bolton DM. Urinary stone disease. In: Tanagho EA, McAninch JW, editors. Smith's general urology. 15<sup>th</sup> ed. McGraw Hill; 2000. p. 291-320.
3. Ueno A, Kawamura T, Ogawa A, et al. Relation of spontaneous of ureteral calculi to size. Urology 1997; 109: 544-546.
4. Morse RM, Resniak MI. Ureteral calculi, natural history and treatment in an era of advanced technology. J Urol 1991; 145: 263-265.
5. Millen F, Kane CJ. Time to stone passage for ureteral calculi; a guide for patient education. J Urol 1999; 162: 688-691.
6. Kuo RL, Aslan P, Abrahamse PH, et al. Incorporation of patient preference in the treatment of upper urinary tract calculi. J Urol 1999; 162: 1913-8.
7. Miyatake R, Tomiyama Y, Murakami M, et al. Effects of isoproterenol and butylscopolamine on the friction between an artificial stone and the intraureteral wall in rabbit. J Urol 2001; 166: 1083-1087.
8. Vermue NA, Den Hertog A. The action of prostaglandins on ureter smooth muscle of guinea pig. Eur J pharmacology 1997; 142: 163-7.
9. Bradley JU, Lowrence L. Drug used in the treatment of asthmian. In: Hardman JG, Limbird EL, editors. Goodman and Gilman's the pharmacologic basis of therapeutics. Tenth ed. McGraw Hill; 2001. p. 733-751.

10. Becker AJ, Stief CG, Meyer M, et al. The effect of the specific phosphodiesterase-IV-inhibitor rolipram on the ureteral peristalsis of the rabbit and in vivo. J Urol 1998; 160: 920-925.
11. Aquino RD, Prodigalidad AM, Reyes JAC, et al. Invitro relaxation of rabbit ureter using theophylline to facilitate passage of an artificial ureteral stone. Philippine Journal of Urology 1993; 3: 3-8.

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