

Effect of Tamsulosin on Biomarkers after Ureteral Stones LithotripsyMohammed Khalid Abood^{*}, Wasan Abd Alkarim abass^{**}, Ammar Fadil^{***}^{*} Department of Clinical Pharmacy, College of Pharmacy, Al-Mustansiriyah University^{**} Department of Clinical Laboratory Science, College of Pharmacy,

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Abstract:

Since the aurora of civilization, urolithiasis has plagued humans. Defective drainage due to urinary tract obstruction at the narrowest part (ureterovesical junction, ureteropelvic junction, and near the pelvic brim) via stones will eventually cause the agonizing renal colic pain. Therapeutic managements of urolithiasis to relief acute colic pain are the primary objective. Non-steroidal anti-inflammatory drugs are the most commonly used drugs as suggested by many studies. It is very important to consider side effects of the drugs used in the treatment of colic pain.

In order to preserve renal function and to relief obstruction, medical expulsion therapy are used for ureteral calculi as a conservative management. These medications will aid the passage ureteral calculi, an area that currently seems to be a field for continuous investigation. The Aim of this Study is to compare renal biomarkers before and after Lithotripsy and to evaluate the effect of Tamsulosin on these biomarkers in patients with ureteral stones.

We concluded that, there were significant differences in the clinical outcomes obtained after using tamsulosin for 14 days in patients with ureteral stones who underwent lithotripsy compared with those patients who were not used tamsulosin; the levels of KIM-1, and serum urea were decreased significantly (p value <0.05) while the levels of ALP and serum sodium show an improvement when compared to patients who were not used tamsulosin but it's results were statistically not significant.

Keywords: Ureteral stones, lithotripsy, tamsulosin.

تأثير علاج التامسولوسين على المؤشرات الحيوية بعد تفتيت حصى الحالب

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 فرع الصيدلة السريرية كلية الصيدلة الجامعة المستنصرية
 فرع العلوم المخبرية السريرية كلية الصيدلة الجامعة المستنصرية
 لية الطب الجامعة المستنصرية

:

البولية بتلت البشرية بمرض حصى الكلى والحالب. ضيق منها (الحالب يتقاطع) في نهاية

الهدف الرئيسي من الإل العلاجية ل غير الستيرويدية هي أكثر العلاجات شيوعا للأدوية المستخدمة .
 هتخفيف آلام العديد من الدراسات من المهم جدا الانتباه للأثار الجانبية الحالب يجب ، هذا المجال حاليا هو قيد هذه الأدوية .
 التحقيق المستمر.

ن الهدف من هذه الدراسة هو مقارنة العلامات البيولوجية لمرضى الحالب قبل وبعد التفطيت بالموجات لتقييم تأثير عقار التامسولوسين على هذه العلامات البيولوجية عند المرضى المصابين بحصى الحالب. أظهرت هذه الدراسة استخدام علاج التامسولوسين لمدة 14 يوما لمرضى حصى الحالب الذين يخضعون لتفتيت الحصى بالموجات وعند مقارنة نتائج هؤلاء المرضى بمجموعة المرضى الذين لم يستخدموا علاج التامسولوسين فان مستويات اليوريا و ال KIM-1 يون الصوديوم و نزييم ال ALP قد تحسنت ولكن النتائج لم تكن مهمة.

Introduction:

Urolithiasis is multi-factorial diseases that result from the combined influence of epidemiological, biochemical and genetically risk factors. The prevalence of urolithiasis is approximately 2-3 % in the general population, and the estimated lifetime risk is approximately 12 % for white males [1].

Urinary stones have high recurrence rates approach 50% at 10 years [2]. Urinary stone diseases are 2-3 times more common in males than in females. It occurs more often in adults than in elderly patients, and more often in elderly than in children. White individual are affected more than Asian ethnicity, who are affected more than blacks. In addition, urolithiasis occurs more frequently in hot, arid areas than in temperate regions. Decreased fluid intake and consequent urine concentration are among the most important factors affecting stone formation. Certain medications are associated with increased risk of urolithiasis. Dietary oxalate is another possible cause, but the role of dietary calcium is less clear, and calcium restriction is no longer universally recommended [3]. Although mortality from urinary stone diseases is rare, there is a significant rate (28%) of renal deterioration with certain stone types. [4]

Materials and Methods:

Patients:

A total of 20 patients (age from 25-60 years) with stones located in the ureter, admitted in Al-Yarmouk teaching hospital in Baghdad, Iraq from November 2013 to October 2014, were included in the study. Patients who were admitted to undergo

extracorporeal shock wave lithotripsy (ESWL) were approached and those with ureteral stones were selected.

The study sample consists of 30 participants enrolled according certain specification, and then subdivided into three groups:

Group-1: Include 10 patients with ureteral stone taking tamsulosin for 14 days & then treated with lithotripsy.

Group-2: Include 10 patients with ureteral stone taking no medication and then treated with lithotripsy.

Group-3: Include 10 normal individual to compare their data with patients as control group.

These subdivisions done after completion of matching process for each groups with each other regarding to: age, no co existing chronic diseases and stone locations.

The intake of the drugs was for 14 days followed immediately by extracorporeal shock wave lithotripsy for each sample groups, and there were no missing values among the study sample.

Diagnostic Methods

Patients are evaluated by:

- 1- X-ray kidney ureter and urinary bladder (KUB).
- 2- Urine analysis and microscopy.
- 3- Ultrasonography (USG).
- 4- Renal function tests.
- 5- Computed tomography of the urinary tract performed in addition to ultrasonography.
- 6- Intravenous urography [5, 6].

Study Design:

A Modulith SLX-F2 machine equipped with a cylindrical electro-magnetic shock wave source (Storz Medical, Tuttlingen, Switzerland) was

used to perform lithotripsy. All 24 patients received 3000 shocks in 30 minutes with an energy level of 7 kV gradually increased to 9 kV within 500 initial shocks and a mean frequency of 1.5 Hz with a variable focus.

Outcome Parameters and Follow-Up:

Renal biomarkers should be measured before starting therapy with Omnic® (Astellase) for 14 days, and then patients will undergo ESWL followed by second measurement of renal biomarkers after completion of ESWL. The main methods of follow-up were diagnostic

Date of acceptance: 21-5-2015

testing (Alkaline phosphatase, Serum urea, Sodium, and Kidney injury molecules No.1)

Methodology:

Chemicals and Kits:

The following diagnostic kits were used in the study, which are listed with their suppliers in table below (table-1).

Instruments:

The main instruments, devices and tools that were used during the study are listed with their suppliers in table below (table-2).

Table-1: Diagnostic Kits or chemical

Diagnostic Kits or chemical	Supplier	Origin
Alkaline Phosphatase Reflotron® Kit	Roche	USA
Serum Urea Enzymatic Kit	Linear chemicals	Spain
Serum Sodium Enzymatic Kit	Stanbio Laboratory	USA
Kidney Injury Molecule no. 1 ELISA Kit	Cusabio	China

Table-2: Instruments

Instruments	Suppliers	Origin
Water bath	KK	Malaysia
Centrifuge	KK	Malaysia
Ultraviolet – visible spectrophotometer	Apel DP 303	Japan
Reflotron	Roche	USA

Blood specimens:

Five milliliters (5 ml) of venous blood samples were drawn from each patient before starting therapy and after ESWL. The blood specimens were collected from patients and healthy individuals. The collected samples were transferred into clean plain test tubes, left at room temperature (25°C) at least 15 minutes to clot, then centrifuged and the serum was extracted to be used for biochemical assessments. The measured parameters include: serum sodium, alkaline phosphatase, serum urea, and kidney injury molecules No. 1 levels.

Statistical Analysis:

For data encoding and analysis; SPSS (statistical package for social science version 16.0, SPSS Inc. Chicago, Illinois, USA) was used and the test of significance association was done by one way ANOVA tests and the cutoff point of significance was (< 0.05) *P* value.

Results and Discussions:

Demographic Profile:

From 20 patients, 10 were treated with tamsulosin, there was no significant difference between and within groups of the study sample and it was matched in

regarding age and gender variables (table-3).

Baseline marker values:

Descriptive data were obtained from study sample include blood urea (Linear chemicals, Spain), alkaline phosphatase (Roche, USA), sodium (Stanbio Laboratory, USA), and KIM-1(Cusabio, China) were tested before and after ESWL in those using or not using tamsulosin. Patients with ureteral stones have high blood urea compared to control group. That result regard logical as obstruction usually lead to increase urea levels in blood. Also, the alkaline phosphatase level was elevated among group with ureteral stones in comparing to control group. The level of Sodium is high in ureteral stone group, in comparing to control group (table-4).

Comparison of the effect of ESWL on biomarkers between renal and ureteral stone groups after 2 weeks therapy:

To assess the effect of the ESWL on blood urea, alkaline phosphatase, Serum sodium and KIM-1, one way ANOVA test, and paired sample t test were used to assess significant association between ESWL with each variables (blood urea, Serum Sodium, ALP, and KIM-1) among study sample.

According to these results, group of patients with ureteral stones get more benefit from ESWL than patients group with renal stones, and the results were statistically significant (p value <0.05) specially for renal function and KIM-1 which regard specific indicator for renal injury, while ALP and blood ions it come better after ESWL, but the results were not statistically significant (table-5 and table-6).

Furthermore, the results in this study are not compatible with the studies of Namık Kemal Hatipo lu, *et, a.l*^[7] and Nader Fahmy *et, a.l*^[8] due to two main reasons. The first reason was that, they measure KIM-1 levels in urine while in the

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present study we measure KIM-1levels in serum. The second reason was they select patients with renal stones and all these patients received at least 3500 shock at 9-12 kV.

On the other hand, this study agreed with the study of Muhammed Ali Shaker *et, al.*^[9] as the level of ALP would be increased after ESWL as a result of renal injury. Also this study agreed with the studies of Karlsen and Berg, S. Sen *et, al.*^[10] and Masao Yokoyama *et, al.*^[11] as the levels of the serum creatinine and serum urea would be decreased after ESWL.

Comparison of the effect of ESWL and tamsulosin on biomarkers between renal and ureteral stone groups after 2 weeks therapy:

Treatment with medical expulsion therapy, especially tamsulosin, for ureteral stones has been demonstrated to be effective in several reports. Tamsulosin is associated with a greater likelihood of ureteral stone elimination, less pain, and faster elimination compared with patients who were not used tamsulosin ^[12-19]. To assess the effects of ESWL in combination with tamsulosin on serum urea, alkaline phosphatase, serum sodium and KIM-1, one way ANOVA test, and paired sample t test were used to assess significant association between each independent factors (ESWL, and tamsulosin), with each variables among study sample.

As we seen in these results, when comparing means of blood urea between groups of patients who use tamsulosin to those who are not, the improvement in the levels of blood urea were more better in the groups who use tamsulosin in comparing to those who are not used tamsulosin (the decrease in the means of blood urea among patient who use tamsulosin were 10.22) and the result was highly significant when tested by ANOVA (p value <0.05).

Regarding ALP, the improvement was only occurring among group's patients

who use tamsulosin and the decrease in the means was 22 degree but the results were not significant (p value >0.05). Regarding serum sodium in comparing between who use and who were not uses tamsulosin, the result was nearly similar and there is an improvement in the blood levels of these ions but the results were not significant (p value >0.05).

Special attention was given to KIM-1; there is no improvement in the level of KIM-1 among groups of patients

who were not used tamsulosin and the means was similar before and after ESWL. On the other hand, the group who were used tamsulosin get better results and the improvement in KIM-1 was significant statistically (p value <0.05). When we compare KIM-1 values after ESWL alone and KIM-1 values after ESWL and tamsulosin, the difference in these values attributed to the effect of tamsulosin (table-7 and 8).

Table-3: Matching process between and within groups of study sample in regard to age and gender, ANOVA test was used for comparison.

Group	No.	Age		Gender % Female: male
		Mean	SD	
Ureteral stone	20	38.23	± 5.1	48%: 52%
Normal volunteer	10	38.35	± 5.12	49%: 51%
Total	30	37.73		

Where; $F = 1.2, df = 2, p$ value > 0.05

Table-4: Means and standard deviation for each variable among study sample.

Ureteral stone group	Bl.urea	ALP	Na
Means	48.17	100.9	145.5
SD	14.9	14.7	13.2
Control group	Bl.urea	ALP	Na
Means	37.35	80.05	139.3
SD	4.01	10.08	4.4

Where; ALP= alkaline phosphatase U/L, Bl.urea= blood urea mg/dL, Na= Sodiummmol/L.

Table-5: Comparison of means and standard deviation for different variables between the groups of study sample.

Group		Variables			
		Bl. urea(base line)	Bl. Urea (after 14 days)	ALP (base line)	ALP (after 14 days)
Ureteral stone	Mean	48.1	39.05	100.9	92.1
	SD	14.9	12.3	14.7	17.4
Group		Variables			
		Na (base line)	Na (after 14 days)	KIM-1 (base line)	KIM-1 (after 14 days)
Ureteral stone	Mean	145.5	130.5	2.1	2.06
	SD	13.2	9.7	0.64	0.69

Where; ALP= Alkaline phosphatase U/L, Bl.urea= blood urea mg/dL, ESWL= extracorporeal shock wave lithotripsy, KIM-1= Kidney injury molecule no. 1ng/ml, Na= Sodium mmol/L.

Table-6: ANOVA test of different variables among study sample in regard to the groups of patients.

Variables	F	sig
Bl.urea before	10.01	0.002
Bl.urea after	8.54	0.005
ALP before	14.84	0.000
ALP after	2.15	0.146
Na before	13.06	0.001
Na after	1.06	0.308
KIM-1 before	3.7	0.06
KIM-1 after	19.5	0.000

Table-7: Comparison between different variables of the study sample in regard to use of the tamsulosin.

Tamsulosin		Variables			
		Bl. urea (base line)	Bl. Urea (after 14 days)	ALP (base line)	ALP (after 14 days)
Not Use	Mean	45.15	39.05	93.8	93.2
	SD	14.21	12.51	17.7	18.02
Use	Mean	42.27	32.05	109.47	87.47
	SD	12.34	8.52	19.4	16.8
Tamsulosin		Variables			
		Na (base line)	Na (after 14 days)	KIM-1 (base line)	KIM-1 (after 14 days)
Not use	Mean	140.7	133.6	3.04	3.04
	SD	11.2	10.6	2.63	2.1
Use	Mean	148.9	131.4	2.63	2.1
	SD	9.02	8.3	0.97	0.96

Where; ALP= Alkaline phosphatase U/L, Bl.urea= blood urea mg/dL, ESWL= extracorporeal shock wave lithotripsy, KIM-1= Kidney injury molecule no. 1ng/ml, Na= Sodium mmol/L.

Table-8: ANOVA test of significance for different variables in regard to using of tamsulosin.

Variables	F	sig
Bl.urea before	0.93	0.33
Bl.urea after	8.54	0.005
ALP before	14.84	0.000
ALP after	2.15	0.146
Na before	13.06	0.001
Na after	1.06	0.308
KIM-1 before	3.7	0.06
KIM-1 after	19.5	0.000

Conclusions:

After using tamsulosin for 14 days in patients with ureteral stones who underwent lithotripsy compared with those patients who were not used tamsulosin; the levels of KIM-1 and serum urea decreased significantly while the level of ALP and Serum Sodium show an improvement but it's statistically not significant.

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Date of acceptance: 21-5-2015

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