Renoprotective effect of mannitol infusion during extracorporeal shock lithotripsy

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ABSTRACT

الأهداف: تقييم دور إعطاء مادة المانيتول لتخفيف أو منع الضرر الكلوي الذي يصاحب عملية التفتيت بأمواج الصدم (ESWL) وقياس التغيرات في مؤشر ممانعة الكلية (RI).

الطريقة: خلال الفترة ما بين فبراير 2006م وحتى سبتمبر 2006م، تم تشخيص 38 مريض إشعاعياً (28 رجل – 10 امرأة) تتراوح أعمارهم ما بين 20–50 عام، خضعوا لعلاج باستخدام جهاز تفتيت الحصى (ESWL) من خارج الجسم في وحدة التفتيت (ESWL) بقسم الجراحة البولية – مستشفى الجراحات التخصصية – بغداد – العراق. حيث كان الـ38 مريض يشكون من حصى في الكلى بحجم (10-20mm). تم تقسيم المرضى إلى: مجموعة تحت المراقبة وتتكون من (20 مريض) ومجموعة المانيتول تحت العلاج (18 مريض). وقد تم قياس التغيرات في مؤشر ممانعة الكلية (RI) لجميع المرضى مباشرة قبل وبعد إجراء عملية التفتيت بأمواج الصدم (ESWL)، وكذلك بعد 3 و7 أيام، في حين تم حقن المرضى في مجموعة المعالجة بمادة المانيتول بـ(0.5gm/kg) خلال عملية التفتيت ولم يتم إعطاء مجموعة السيطرة أي ماده خلال عملية التفتيت. تمت دراسة التغيرات في مؤشر ممانعة الكلية (RI) إحصائيا مع مقارنة النتائج في داخل المجموعة الواحدة وبين المجموعتين.

النتائج: كان هناك وضوح كبير في تغيير المؤشرات القياسية لمقاومة الكلى فور الخضوع للمعالجة بـ(ESWL)، ثم بعد 3 و7 أيام. كما تبين أنها ازدادت عن البداية بالقيم من 0.5875 إلى 0.6500، 0.6300، 0.6245 على التوالي. وقد أظهرت مجموعة المانيتول تغييرات أقل بكثير، وعلى الرغم من ذلك لا يزال التغير كبير من 0.5850 إلى 0.6061، 0.6022 و0.5967 على التوالي، هذا الارتفاع في مقاومة الكلى المؤشر في مجموعة المراقبة عند مقارنتها بمجموعة المانيتول فيه تغير كبير من الناحية الإحصائية.

خاتمة: مادة المانيتول تعمل على حماية الكلى عندما تعطى خلال عملية التفتيت (ESWL)، كما يتضح من الناحية الإحصائية انخفاضا كبيرا في مؤشر مقاومة الكلى (RI).

Objectives: To evaluate the role of mannitol infusion in preventing or ameliorating renal injury that accompanies shock wave lithotripsy as measured by changes in resistive index (RI).

Methods: Between February and September 2006, 38 patients (28 men and 10 women) underwent extracorporeal shock wave lithotripsy (ESWL) for radiologically documented renal stones in The Surgical Specialties Hospital ESWL unit, Baghdad, Iraq. The 38 patients aged 20-50 years with renal stones of 10-20 mm size, scheduled for ESWL therapy, were divided into a control group (20 patients) and mannitol group (treatment group of 18 patients). All patients had their renal RI measured before ESWL, immediately after ESWL, then 3 and 7 days later. While patients in the mannitol group were given 0.5 gm/kg mannitol infusion during lithotripsy, the control group patients were given nothing. Changes in renal RI in both groups were evaluated statistically within the group and between the 2 groups.

Results: A significant rise in renal RI was found in the control group immediately after ESWL, then 3 and 7 days after. It increased from an initial value of 0.5875 to 0.6500, 0.6300, and 0.6245. The mannitol group showed fewer changes, yet still significant from 0.5850 to 0.6061, 0.6022, and 0.5967. This elevation of renal RI in the control group when compared to the mannitol group was statistically significant.

Conclusion: Mannitol has a renoprotective function when given during ESWL, as evidenced by the statistically significant reduction in renal RI.

Saudi Med J 2009; Vol. 30 (6): 767-770

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Received 4th February 2009. Accepted 29th April 2009.

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In most of the centers around the world, extracorporeal shock wave lithotripsy (ESWL) is considered the preferred first line treatment option for patients with renal stones, as it is safe, and minimally invasive, however, recent studies demonstrated a detrimental

effect on renal cellularity and vasculature with the vascular damage being the primary event. This effect can be acute or chronic, and is related to hemorrhage, ischemia, and free radical formation.[1-6] Morphological studies using both magnetic resonance imaging and quantitative radionuclide renography have suggested that 63-85% of all ESWL patients treated with unmodified HM3 lithotripter exhibit one or more forms of renal injury within 24 hours of treatment. The 2 most common renal side effects found immediately after ESWL are hemorrhage and edema, within or around the kidney. Frequently, the kidney is enlarged and there is a loss of corticomedullary differentiation suggesting the presence of acute intrarenal edema.[7] Only one histopathological study has documented acute changes in the kidney and surrounding tissues of an ESWL treated human stone former. Renal biopsy obtained within one week of ESWL revealed marked tubular, vascular, and interstitial changes that were localized to the plane of the pressure wave.[4,8] Most renal corpuscles in this zone were disrupted, whereas the rest of the nephrons showed mild degenerative changes and an accumulation of hemosiderin granules and cast material. Microvascular alterations included dilation of veins, with evidence of endothelial damage and thrombus formation.[8] The aim of the study is to assess the acute renal injury that accompanies ESWL therapy for renal stones, and evaluate the role of hypertonic mannitol infusion during the process in preventing or ameliorating this renal injury, as measured by changes in renal resistive index (RI).

Methods. Between February and September 2006, 38 patients (28 men and 10 women) underwent ESWL for radiologically documented renal stones in The Surgical Specialties Hospital ESWL unit, Baghdad, Iraq. They were randomized into 2 groups. Eighteen patients were given 0.5 g/kg mannitol intravenously immediately before the beginning of ESWL, and the other 20 patients acted as control. The procedure was explained to all patients, and the Ministry of Health ethical committee approval was obtained. The renal RI was measured for each patient before ESWL, immediately after ESWL, 3 days, and one week after ESWL using Siemens, Sonoline Versa pro US machine (Siemens, Erlangen, Germany) with 3.5 MHZ transducer. The study inclusion criteria were a solitary radio-opaque renal stone of 10-20 mm in patients undergoing ESWL for the first time. Patients with pre-existing renal disease, hydronephrosis, medical diseases such as hypertension or diabetes, taking medications that interferes with study results (non-steroidal anti-inflammatories, Aminophyllin, allopurinol, or calcium channel blockers, and beta blockers), and those with abnormal bleeding profile, were excluded from the study. A full assessment was carried out for each patient. This included history, vital signs, urine exam, renal function, bleeding profile, and a review of ultrasonic and excretory urogram results to document stone size and location, and to exclude obstruction. An intravenous access was secured, and mannitol infusion was started. This step was omitted in the control group. The ESWL was performed with Lithostar Multisystem (Siemens, Erlangen, Germany), giving 3500 shock waves at 15.1 KV with a frequency of 2 shock waves per second. The same radiologist performed Doppler ultrasound examinations in all patients. The signals were measured over the interlobar and arcuate arteries, the RI was calculated as:

$$RI = \frac{\text{(systolic velocity – diastolic velocity)}}{\text{systolic velocity}}$$[4]

The RI was measured in 3 areas near the stone, and the mean was recorded. Patients were followed by US of kidney, ureter and bladder, and CT scan for perinephric hematoma formation.

Using the Statistical Package for Social Sciences version 10.0 (SPSS Inc., Chicago, IL, USA), data obtained were analyzed statistically using Chi-square test, t-test for equality of means, and paired sample test as appropriate. A p-value of <0.05 was considered significant.

Results. The age, stone size, and gender distribution between the 2 groups is shown in **Table 1**. There was no significant relationship between gender and RI,

Table 1 - Age and stone size for both the control and mannitol groups.

Groups	N	Age in years Mean (SD)	Stone size in mm Mean (SD)	Gender (n)	(pre [R 0] ESWL RI) Mean (SD)	(post [R 1] ESWL RI) Mean (SD)
Control	20	35.75 (5.72)	14.9 (2.46)	Males (14)	0.5793 (0.04376)	0.6407 (0.04698)
				Females (6)	0.6067 (0.01862)	0.6717 (0.02229)
Mannitol	18	34.1667 (4.409)	15.05 (2.95)	Males (14)	0.5793 (0.03075)	0.6014 (0.03348)
				Females (4)	0.6050 (0.02517)	0.6225 (0.03096)

ESWL - extracorporeal shock lithotripsy, RI - resistive index, SD - standard deviation

Table 2 - The relationship of gender to pre, and post ESWL values of RI in both groups.

Groups	t-test for equality of means		
	t-test	df	*P*-value (2-tailed)
Control			
RI 0	1.963	17.967	0.065
RI 1	1.524	18	0.145
Mannitol			
RI 0	1.523	16	0.147
RI 1	1.126	16	0.277

ESWL - extracorporeal shock lithotripsy, RI - resistive index, RI 0 - pre ESWL, RI 1 - post ESWL, df - degrees of freedom

Table 3 - Resistive index values for both groups.

Groups	RI 0 Mean (SD)	RI 1 Mean (SD)	RI 2 Mean (SD)	RI 3 Mean (SD)	RI 01 (%) Mean (SD)	RI 02 (%) Mean (SD)	RI 03 (%) Mean (SD)
Control	0.5875 (0.395)	0.6500 (0.0430)	0.6300 (0.0455)	0.6245 (0.0438)	10.68 (3.059)	7.251 (3.547)	6.302 (2.482)
Mannitol	0.5850 (0.0309)	0.6061 (0.0323)	0.6022 (0.0309)	0.5967 (0.0318)	3.607 (1.409)	2.955 (0.9913)	2.000 (1.317)

RI 0 - pre ESWL, RI 1 - immediately ESWL, RI 2 - 3 days after, RI 3 - 7 days after, RI 01 - difference in RI immediately after ESWL from pre ESWL, RI 02 - difference in RI 3 days after ESWL from pre ESWL, RI 03 - difference in RI 7 days after ESWL from pre ESWL, SD - standard deviation

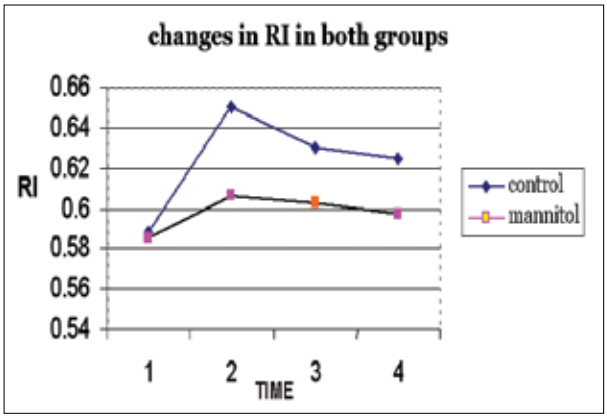

Figure 1 - Renal resistive index (RI) values for both groups at: 1) before extracorporeal shock lithotripsy (ESWL) 2) immediately after ESWL. 3) 3 days after ESWL. 4) 7 days after ESWL.

whether pre or post ESWL, neither in the control nor in the mannitol group (**Table 2**). The values of RI before ESWL in the 2 groups were 0.5875 (0.51-0.63) for the control group and 0.5850 (0.53-0.63) for the mannitol group, and this difference was not significant (p=0.702). To show the effect of mannitol, RI values immediately, 3 days, and 7 days after ESWL, for both groups were

Table 4 - Independent sample test, showing the significant differences in RI changes between the 2 groups at all times.

RI	t-test for equality of means		
	t-test	df	*P*-value (2-tailed)
RI 0	0.388	18	0.702
RI 1	2.568	18	0.019
RI 2	1.843	18	0.082
RI 3	1.669	18	0.112
RI 01	10.392	13.984	<0.001
RI 02	5.876	18	<0.001
RI 03	5.699	18	<0.001

RI 0 - pre ESWL, RI 1 - immediately ESWL, RI 2 - 3 days after, RI 3 - 7 days after, RI 01 - difference in RI immediately after ESWL from pre ESWL, RI 02 - difference in RI 3 days after ESWL from pre ESWL, RI 03 - difference in RI 7 days after ESWL from pre ESWL, df - degrees of freedom,

compared in terms of mere changes and percentages of change. This is illustrated in **Table 3** and **Figure 1**, which demonstrates significantly larger changes in the RI in the control group compared with the mannitol group at all times (**Table 4**).

Discussion. The acute and chronic detrimental effect of ESWL on the kidney has been thoroughly studied. A spontaneously resolving hematuria occurs in almost all patients following ESWL,[2,8,9] while clinically significant perinephric hematoma occurs only in less than 1%.[10] However, serious complications as severe as acute renal failure can occur following ESWL, which are thought to be caused by edema, not obstruction.[11] These are transient changes, but a long standing significant decrease in renal plasma flow (as measured by iodohippurate renal scan) up to 21 months after ESWL has been described by Williams et al.[12] The long term effects of ESWL, such as hypertension and renal impairment are still under investigation, with incidences ranging from 1-8% in different studies.[13,14] It seems logical to relate the long term detrimental effects of ESWL with the degree of initial injury.

In our evaluation, we studied the effect of mannitol infusion in patients undergoing ESWL for renal stones, and whether it can prevent or ameliorate the acute injury. We used changes in renal RI as a measure of degree of renal injury. It clearly demonstrated a consistent and significant rise in renal RI following ESWL in the control group, and this rise is significant in the mannitol group. As renal RI is considered a reliable indicator of renal injury, our study clearly indicates that mannitol has a renoprotective effect when given during lithotripsy. To validate the use of renal RI as a measure

of acute renal injury caused by ESWL, other factors that may affect its value were taken in consideration when selecting patients for the study. Every effort was made to exclude patients with conditions that may affect the renal RI value, such as medical diseases (especially those affecting the renal vasculature), medications like non-steroidal anti-inflammatories, elderly patients, patients with obstructive uropathies, and those with history of previous treatment with ESWL.

As the main injury caused by ESWL is a vascular one, especially in the form of generating oxygen free radicals,[15] many studies evaluated the protective effect of many drugs in patients undergoing ESWL. Ogiste et al[11] studied the role of mannitol in alleviating renal injury during ESWL by measuring changes in the levels of the urinary enzymes ß2-microglobulin and microalbumin as indicators of renal injury, and found a significant decrease in ß2-mincroglobulin excretion after ESWL in patients infused with mannitol during the procedure. Behnia et al[16] from Northwestern University Medical School in Chicago studied the effects of hypertonic mannitol infusion on the hemodynamics of dog kidney when subjected to 50% reduction in blood flow, and found a significant beneficial effect of mannitol infusion on both intact and ischemic kidneys. Feagins et al[17] showed that acute changes in blood pressure following lithotripsy might be attenuated by pretreatment with allopurinol or mannitol administration that can prevent free radical formation. Li et al[15] used nifedipine and allopurinol instead of mannitol as renoprotective agents, and found a significant reduction in renal injury in the treatment group compared to the control group as measured by levels of urinary albumin and ß2-microglobulin.

There is a concern that because mannitol increases renal blood flow, there may be an increased risk of bleeding and hematoma formation after ESWL in the treatment group; none of our patients in both groups developed this complication. Mannitol has relatively benign side effects. This study provides evidence that it has a significant protective effect against the immediate renal damage induced by ESWL. We chose mannitol solution because it is available in Iraq despite the aftermath of sanctions and thereafter. It is available for medical use in 10 and 20% preparations. We recommend its use during ESWL because of its renoprotective effects.

Further future studies and the use of other agents, such as astragaloid that provides significant protection against shock wave-induced renal oxidative injury, should be considered.[18]

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