Serum cytocines values in patients after endoscopic surgery for ureteral lithiasis

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Abstract

Obstructive uropathy due to ureteral stones can cause renal infection and, if left untreated, can cause impairment of renal function. Endoscopic surgery such as ureteroscopy (URS) and laser lithotripsy are the primary therapeutic approach. Cytokines as non invasive markers may have a role to diagnose ureteral damage and infection. *We aimed* to evaluate serum cytokine levels of tumor necrosis factor-a (TNFa) and interleukin-6 (IL6) in patients undergoing URS and holmium laser lithotripsy. The study included 40 patients (male 25 and 15 female) with a mean age of 47 years and 10 healthy blood donors serving as the control group. None of them had any additional systemic diseases, previous insertion of a ureteral double "j" stent or of a nephrostomy tube, neoplasmatic disease ot *renal insufficiency.* Routine urine examination and urine culture were obtained to exclude urinary infection. Preoperatively and 1h, 2h, 24h and 48h postoperatively serum samples of TNF-a and IL-6 were collected and measured. Serum TNFa and IL-6 values were correlated with the other variables measured from blood samples after the URS using paired samples Students t-test with confidence interval 95%. A P value of less than 0.01 was considered statistically significant. Correlation between serum TNF-a and IL6 levels with healthy donors were statistically significant in 1h (0.004), 2h (0.001), 24h (0.001) and 48h (0.001 and 0.001) postoperatively, respectively. In *conclusion,* our study shows that cytokines could be helpful as markers of renal tissue damage. However, further studies are needed to get more accurate results.
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Introduction

The surgical management of ureteric stones has changed over the past few decades because of advances in instruments and techniques. Ureteroscopy and laser lithotripsy are currently the most common treatment options in clinical practice. This surgical procedure is now performed with small caliber endoscopes and devices such as holmium laser [1].

Minimal invasive endoscopic tissue trauma and shock were known to provoke neuroendocrine metabolic reactions. Operative invasiveness could be estimated by measuring any of these reactions expressed by cytocins serum levels. Cytokines such as interleukin-6 (IL-6) and tumor necrosis factor a (TNFa) have been used as indicators of operative invasiveness in the surgical field [2-4].

In the present study, we measured serum IL-6 and TNF a levels to examine the invasiveness of operative procedure, and to determine factors that are responsible for the minimally invasive character of ureteroscopy and laser lithotripsy.

Subjects and methods

A total of forty patients (25 males, 15 females), mean age of 47 (range: 26-68y) with ureteral lithiasis treated with ureteroscopic lithotripsy (USL) and 10 healthy blood donors as the control group were studied. Patients' and control group's characteristics are shown in Table 1. Patients with acute urinary infection or previous intervention with URS, percutaneous lithotripsy or extracorporeal lithotripsy were excluded from the study. All those interventions produce an acute injuries effect and provoke a neuroendocrine metabolic reaction which affect preoperative and postoperative serum cytocine values [5].

TNF-a was measured at after the case. Before and 1h postoperatively and 24h and 48h postoperatively for TNF a while IL-6 levels were measured at 2h postoperatively and 24 and 48h, 2h after serum samples were obtained to evaluate the acute effects of the procedure. The blood samples were centrifuged as soon as possible at 4000rpm for 10min at 4°C. The serum samples were divided into aliquots and stored at -85°C for the assessment performed in weekly intervals. Cytokine concentrations were measured using the commercial Biosource Europe SA IL-6- IRMA and TNF-a- IRMA (Rue de l'Industrie 8 B-1400 Nivelles, Belgium) by immunoradiometric assay (IRMA) methods. The reference range for IL-6 normal values was 6-31pg/mL for healthy controls and for TNF-a 5pg/mL respectively.

Table 1. *Clinical characteristics of the 40 patients with ureteric lithiasis treated with holmium laser lithotripsy and the 10 healthy donors of the control group*

	Patients with stones	Control group
Mean age (years) (range)	47 (26-68)	51,05 (31-72)
Gender ♀ / ♂	25/15	6/4
Stone size (cm)	Mean stone size	
0-0,6	6 (10%)	-
0,6-1.00	19 (15%)	-
>1.01	15 (12%)	-
Stone location		
Proximal ureter	7 (13.3%)	-
Midureter	19 (43.3%)	-
Distal ureter	14 (43.3%)	-

Statistical analysis

Statistical analysis was performed using the statistical package SPSS V.11. Statistical analyses of serum TNF-a and IL-6 values of control group and 1h (or 2h for IL-6), 24h, 48h after URS were performed using paired samples Students t-test with confidence interval 95%. A P value of less than 0.01 was considered statistically significant.

Results

The results of the comparative analysis (t-test independent variable the control group) between the two groups of interest were as follows: serum TNF-a levels were statistical significant correlated the control group serum levels with 1h (P=0.004), 24h and 48h (P<0.001) after URS and IL-6 in 2h, 24h and 48h (P<0.001) (Table 2). Distribution of serum IL-6 and TNF-a serum levels and the control group, before and 1h or 2h, 24h and 48h after URS. Correlations and P values <0.001 are shown in Figures 2 for TNF a and 4 for IL-6. In Figures 1 and 3 we demonstrate the distribution of serum TNF-a and IL-6 of 10 healthy volunteers which represents the control group. All patients developped postoperative microscopic haematuria and in 5 of them we observed a macroscopic haematuria. No evidence of infection before and after URS in the urine examination and cultures were found. All cases with hematuria were managed successfully using conservative management. Other complications, such as stone migration, ureteral mucosal injury (abrasion and false passage formation), ureteral perforation and ureteral avulsion were not observed.

Table 2. *Paired samples t test with confidence interval 95%. Independed variable the Control Group of IL 6 and TNFa before and 1h or 2h, 24h, 48h after ureteroscopy*

	Paired differences	STD deviation	STD error mean	95% Confidence interval of the difference		t	df	Sig.(2-tailed)
	Mean			Lower	Upper			
IL6								
Before URS- CG	22.62	19.00	6.00	11.27	36.97	4.00	9	,005
2h after URS-CG	40.61	40.00	13.00	12.97	68.25	3..00	9	,001
24h after URS-CG	36.89	19.00	6,00	24.24	49.53	6.00	9	,001
48h after URS-CG	66.42	46.00	15.00	32.42	100.43	5.00	9	,001
TNF-a								
Before URS-CG	20.05	13.00	4.00	9.43	30.66	5.00	9	,008
1h after URS-CG	41.39	31.00	10.00	17.45	65.32	4.00	9	,004
24h after URS-CG	24.00	10.00	3.00	11.25	25.49	6.00	9	,001
48h after URS-CG	26.25	13.00	4.00	15.66	36.85	6,00	9	,001

Discussion

Minimal invasive surgery for ureteral lithiasis such ureteroscopy and laser lithotripsy have become popular in the field of urology, partly due to their minimally invasive features. The quantification of the operative invasiveness of these procedures has drawn clinical interest. Surgical tissue shocks were known to provoke neuroendocrine-metabolic reactions [6.7].

Epithelial cells form a barrier between submucosa and environment and release the pro inflammatory cytokins and other response molecules to activate the protective mechanisms against the harmful agents like bacteria and toxins. Activated epithelial cells interact also with other cellular elements in the submucosa and at distant locations [8].

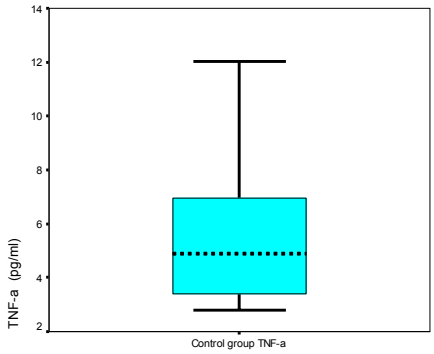

Figure 1. Distribution of serum TNF a levels of control group (10 patients).

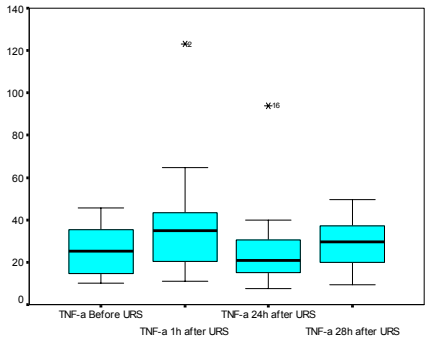

Figure 2. Distribution of serum TNF a levels (40 patients).

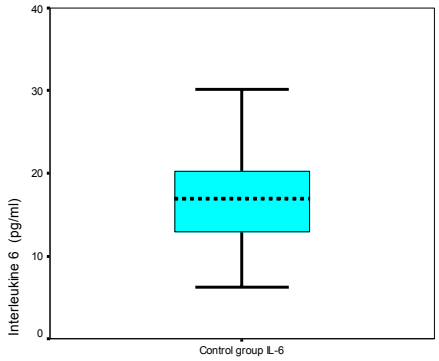

Figure 3. Distribution of serum IL 6 levels of control group (10 patients).

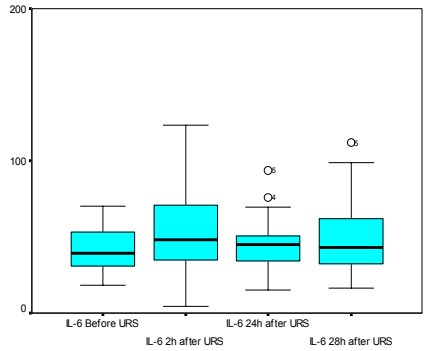

Figure 4. Distribution of serum IL 6 (40 patients).

Among cytokines, interleukin-6 (IL-6) has been used as an indicator of operative invasiveness in the surgical field. [2-4, 9]. This cytokin is a suitable indicator for clinical purposes, because its peak can be measured even on the day after the operation (14 to 20h after surgery). In the study by Igarashi et al (10) serum IL-6 levels differed according to operative procedures. Briefly, open surgery resulted in the most exaggerated increase in serum IL-6 levels, followed by laparoscopic surgery, endoscopy, and ESWL [10].

Tumor necrosis factor-a (TNF-a) is produced by many cells in vivo. Increased and prolonged release of TNF-a is harmful and causes inflammation and tissue damage [11]. According Michie HR et al study in 1988 TNF-a levels increase within 1h and then return to baseline within 3h after endotoxin administration [12].

For IL 6 seams different it increases in 2 to 4h following intravenous endotoxin and not in one hour like TNFa [13]. IL-1 was detected in 60min and high levels occurred in 3h following lipopolysaccaride stimulation of monocytes [14]. Peak levels of IL-1b were also observed at 3h during experimental endotoxemia [15].

Based on this data, in our study the cytokine levels were measured at the first and second hour for TNF-a and IL6 respectively after URS. The significance in the increase of serum TNF-a and IL-6 levels may be due to the sampling method, which serum once at a specific time.

We found significant differences between the cytokine levels before and 1h ($P=0.004$), 24h, 48h ($P<0.001$) after URS and IL-6 in 2, 24 and 48h ($P<0.001$) after URS. This undeniable increase after URS may be the result of the ureteroscopy or the irritation caused by the stone itself. This finding supports that cytokines are produced locally. This strongly significance in the increase of serum TNF-a and IL-6 levels may be due to the sampling method, which collect serum once at a specific time.

As indicated in Table 2 the mean value for serum IL-6 before URS was 22.62pg/mL and 40.61, 39.89 and 66.42 for 2, 24 and 48h after URS and for TNFa the values was 20.05, 41.39, 24.00 and 26,25 for before URS 1,24 and 48h postoperatively.

In conclusion, our study confirmed that serum IL-6 and TNF-a levels are affected by simple tissue injury under aseptic conditions at the time of minimal invasive surgery as ureteroscopy and laser lithotripsy. Further studies that measure the cytokine levels at various intervals after the URS treatment may help to investigate the association between cytokine levels and URS and lithotripsy treatment.

The authors declare that they have no conflicts of interest.

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