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ORIGINAL PAPER

The influence of percutaneous nephrolithotomy on human systemic stress response, SIRS and renal function

Pengfei Shen · Wuran Wei · Xiaochun Yang · Hao Zeng · Xiong Li · Jie Yang · Jia Wang · Jiaoti Huang

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Abstract The objective of this study is to investigate the influences of percutaneous nephrolithotomy (PNL) and open surgery nephrolithotomy on the systemic stress response, SIRS and renal function. Forty patients with kidney calculi were enrolled in the study. Twenty cases were randomized to the PNL group and the other twenty cases to the open surgery group. Levels of C-reactive protein (CRP), interleukin-6(IL-6), β_2-microglobulin (β_2-MG), respiration rate, heart rate, body temperature and white blood cell counts were examined. CRP and IL-6 were measured in all patients pre-operatively and on post-operative days 1, 3 and 6, respectively. There was significant difference in their pre- and post-operation levels ($P < 0.05$), with the peak of CRP and IL-6 observed at post-operative days 3 and 1, respectively. There was significant difference in both CRP and IL-6 between the two groups ($P < 0.05$). At post-operative day 1, there were 5 cases of SIRS in PNL group and 12 cases in open surgery group; there was significant difference between the two groups ($P < 0.05$). Serum β_2-MG levels were measured as the same time as CRP and no significant changes were observed within or between the groups ($P > 0.05$). Urine β_2-MG levels were also measured. There was significant difference between pre- and the first day post-PNL ($P < 0.05$); there was no significant difference between pre- and the third and sixth day post-PNL ($P > 0.05$). There was significant difference between pre- and first and third day post-open surgery ($P < 0.05$); but there was no significant difference between pre- and the sixth day post-open surgery ($P > 0.05$). There was significant difference between two groups at the first, third and sixth days ($P < 0.05$). **Conclusions:** The systemic stress response is activated both in PNL group and open surgery group to some extent. The degree of stress response of PNL is lower than that of open surgery, proving the advantages of PNL with reference to serum immunology. There were cases in both the groups with SIRS, but the degree of SIRS in PNL group was lesser than the other group. Both the groups have no obvious effect on glomerular filtration function after operation and have effect on renal tubular reabsorption in the early stage after operation; but the recovery of the PNL group is faster than the open surgery group. It is thus shown that PNL is much safer and more feasible and has lesser effect on renal function.

Keywords Percutaneous nephrolithotomy · Systemic stress response · C-reactive protein · Interleukin-6 · β_2-Microglobulin · SIRS

P. Shen · W. Wei · X. Yang · H. Zeng · X. Li · J. Yang · J. Wang (✉)
Department of Urology, West China Hospital, SiChuan University, ChengDu 610041, China
e-mail: cdhx510@163.com

J. Huang
Department of Pathology and Laboratory Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Introduction

Urinary stones can be caused by multiple factors and may exist in any part of the urinary system with renal calculus being the most common [1, 2]. Currently, percutaneous nephrolithotomy (PNL) and open surgery are the main treatment modalities for renal calculus [3].

Both open surgery and minimally invasive surgery (PNL) can produce great influences to the body because of trauma, pain, infection, inflammation, etc. Stress response may lead to the elevation of inflammatory factors, such as

the acute phase C-reactive protein (CRP), cytokines interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-2 (IL-2), interleukin-10 (IL-10), TNF-α, etc. IL-1, IL-6 and TNF-α are critical anti-inflammatory cytokines [4]. IL-6 is the key factor and can promote liver cells to secrete CRP, enhances phagocytosis of cells and plays an important role in tissue repair [5, 6]. Under different types of wounds and stimulus, the body may experience systemic inflammatory response syndrome (SIRS). In this process, the inflammatory cells release inflammatory mediators under various stimuli. Normally, all of them are defensive mechanisms of the body after trauma and they will subside after wounds healing. However, if the inflammatory response is excessive or the duration of reaction is too long, the body could enter an abnormal state and if the patient's condition further deteriorates, multiple organ dysfunction can occur as a result [7–9].

Any trauma of kidney could affect the function of this kidney. Because β_2-microglobulin (β_2-MG) can cross glomerular membrane through filtration but cannot be secreted by renal tubules, factors that affect glomerular filtration function can affect the serum β_2-MG level. Therefore, serum β_2-MG level can be used as a marker of the glomerular filtration function and urine β_2-MG level can be used as a marker of renal tubular damage [10–12].

This study was designed to identify the effects of PNL on the body's stress response and renal function, so as to make a comprehensive and objective evaluation of the clinical treatments and risks for patients.

Patients and methods

Patients

Forty patients with renal calculi were enrolled in the study from June 2008 to December 2008 in the West China Hospital. 20 patients (10 males and 10 females) were randomly distributed to the percutaneous nephrolithotomy group (PNL group or experimental group); the other 20 patients (9 males and 11 females) were randomly distributed to the open surgery (nephrolithotomy) group (open surgery group or control group). The mean age of PNL group was 46 years (ranging 34–65 years); the mean age of open surgery group was 45 years (ranging 35–66 years). Patients consented for the study, which was approved by the local ethics committee. Characteristics of the two patient groups are shown in Table 1. There was no statistically significant difference between the two groups in the pre-operative parameters analyzed, including sex, age, urinary tract infection (UTI), BUN, Cr, ALT and AST.

Table 1 Characteristics of the two patients groups

	PNL group	Open surgery group	*P* value
Sex (M/F)	10/10	9/11	NS
UTI (Y/N)	15/5	16/4	NS
Age (years)	46 ± 9.8	45 ± 9.3	NS
BUN (mmol/l)	5.67 ± 2.01	5.86 ± 1.85	NS
Cr (μmol/l)	73.7 ± 15.6	81.9 ± 18.2	NS
ALT (IU/l)	22.2 ± 7.3	21.4 ± 7.5	NS
AST (IU/l)	22.8 ± 8.3	22.6 ± 5.4	NS

N no, *Y* yes, *NS* non-significant

Data are presented as mean ± standard deviation

Patient management

All patients received general anesthesia. The anesthetic time of the PNL group (143.8 ± 14.9 min) was shorter than that of the open surgery group (154.3 ± 33.7 min) ($P < 0.05$). Calculus of the experimental group was removed by PNL; calculus of the control group was removed by pyelonephrolithotomy, anatrophic nephrolithotomy, radial nephrolithotomy or partial nephrectomy; the operative time of the PNL group (118.0 ± 19.1 min) was shorter than that of the open surgery group (132.8 ± 33.7 min) ($P < 0.05$).

A 15 cm inclined lumbar cut through the twelfth rib was adopted to all patients in the open surgery group. The incision was closed with silk sutures. A double J tube (Fr6) was placed in the ureter in all open surgery patients. And average hospital stay was 8 days in this group. The puncture spot of the PNL group was above or below the twelfth rib in the back. The access was gradually expanded to Fr24 with a set of fascial dilaters. A double J tube (Fr6) was also placed in the ureter in the PNL group. Average retention time of nephrostomy tube (Fr14) was 5 days and average hospital stay was 7 days in this group.

If there was a urinary tract infection, cephalosporin or quinolone antibiotics would be used in advance. Antibiotics were used routinely during operation. It should be stopped within 48 h after operation. If a patient was stricken with fever or had a surgical infection, it should be continued.

Samples management

Levels of serum CRP, IL-6, β2-MG and urine β2-MG were examined the day before operation as baseline and on the first, third and sixth days after operation. The serum samples were frozen within 2 h of blood withdrawal. The temperature of blood samples stored was below 4°C. Blood and urine samples were tested in the Clinical Laboratory, Department of West China Hospital. Respiration rate (R),

heart rate (HR), body temperature (T) and white blood cell counts (WBC) were recorded on the first day after operation.

Statistical analysis

SPSS16.0 software was used to analyze the data. Data were expressed as mean ± standard deviation (M ± SD). The differences between the two groups of serum and urine parameters were tested by the One-way ANOVA test. Comparison of SIRS between the two groups was tested by Chi-square test.

Results

Serum CRP and IL-6

The serum CRP levels in PNL group on the day before operation and the first, third and sixth days after operation, respectively, were 2.30 ± 0.50 mg/l, 18.79 ± 3.65 mg/l (vs pre-operation, $P = 0.000$), 29.72 ± 5.83 mg/l (vs pre-operation, $P = 0.000$), 14.34 ± 2.31 mg/l (vs pre-operation, $P = 0.000$); there was statistically significant difference in the serum CRP levels between pre- and post-operation samples ($P < 0.05$). The serum CRP levels in the open surgery group on those days were 2.27 ± 0.65 mg/l, 48.33 ± 9.60 mg/l (vs pre-operation, $P = 0.000$), 93.05 ± 18.11 mg/l (vs pre-operation, $P = 0.000$), 44.17 ± 5.94 mg/l (vs pre-operation, $P = 0.000$); there was statistically significant difference in the serum CRP levels between pre- and post-operation samples ($P < 0.05$). The maximum levels in both the groups were observed on the third day after operation. There was statistically significant difference between the two groups when serum CRP levels were compared on the same post-operative days ($P = 0.000$, $P = 0.000$, $P = 0.000$, respectively) (Fig. 1).

Levels of serum IL-6 in the PNL group the day before operation and on the first, third and sixth days after operation, respectively, were 2.56 ± 0.70 pg/ml, 34.86 ± 2.15 pg/ml (vs pre-operation, $P = 0.000$), 25.01 ± 1.46 pg/ml (vs pre-operation, $P = 0.000$), 13.53 ± 2.71 pg/ml (vs pre-operation, $P = 0.012$); there was statistically significant difference between pre- and post-operation samples ($P < 0.05$). The serum IL-6 levels of the open surgery group on those days were 2.64 ± 0.66 pg/ml, 98.49 ± 6.47 pg/ml (vs pre-operation, $P = 0.000$), 53.10 ± 4.20 pg/ml (vs pre-operation, $P = 0.000$), 30.10 ± 1.71 pg/ml (vs pre-operation, $P = 0.000$); there was statistically significant difference between pre- and post-operation samples ($P < 0.05$). The maximum levels in both the groups were observed on the first day after operation. There was statistically significant difference in IL-6 levels between the two groups on the same post-operative days ($P = 0.000$, $P = 0.000$, $P = 0.003$, respectively) (Fig. 2).

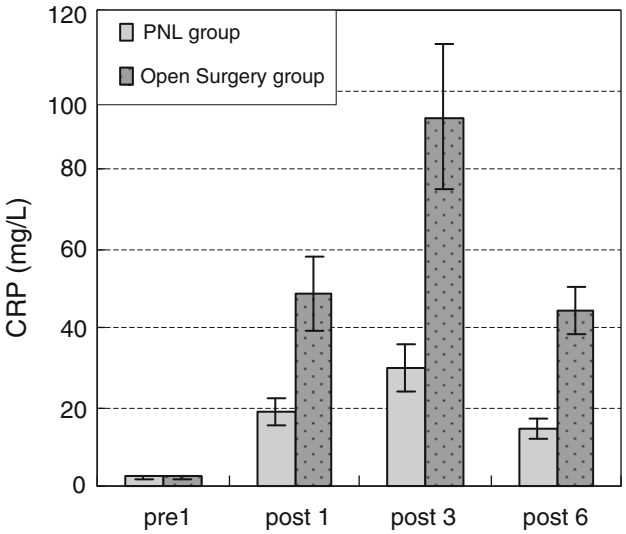

Fig. 1 CRP in PNL and open surgery group

SIRS

On the first day after operation, there were 5 cases of SIRS in the PNL group and 12 cases in the open surgery group; there was statistically significant difference between the two groups ($P < 0.05$). Patients in the two groups had more common abnormal heart rate and respiration rate, increased body temperature and WBC. Fifty percent (10/20) patients of PNL group and 80% (16/20) in the open surgery group had abnormal heart and respiration. One patient in the open

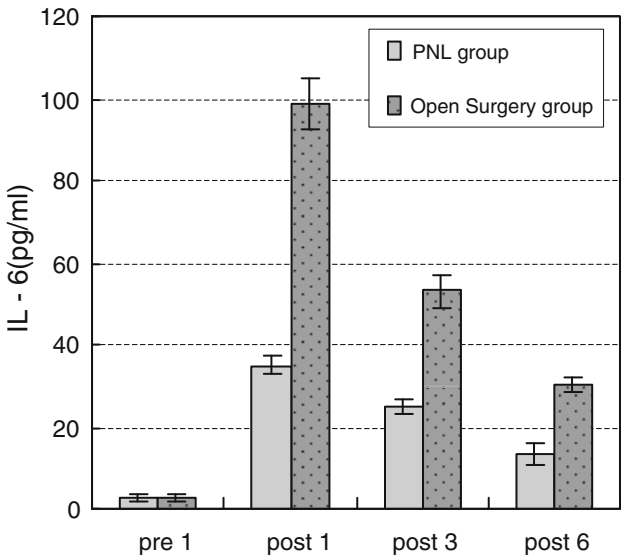

Fig. 2 IL-6 in PNL and open surgery group

Table 2 Diagonsis of SIRS in the two groups

	PNL group ($n = 20$) (%)	Open surgery group ($n = 20$) (%)
T > 38°C	4 (17)	5 (13)
HR > 90/min	10 (41)	16 (41)
R > 20/min	7 (29)	14 (36)
WBC > 12.0 × 10^9/l	3 (13)	4 (10)
SIRS	5 (25)	12 (60)

T body temperature, *HR* heart rate, *R* respiration rate, *WBC* white blood cell

surgery group and none in the PNL group had a body temperature of more than 39°C. No patient in either group had heart rate more than 110/min, respiration rate more than 24/min or WBC more than 16.0 × 10^9/l (Table 2).

Serum and urine β_2-MG

Levels of serum β_2-MG in the PNL group on the day before operation and on the first, third and sixth days after operation were 2.0240 ± 0.3579 mg/l, 1.9365 ± 0.2811 mg/l (vs pre-operation, $P = 0.781$), 2.0750 ± 0.4354 mg/l (vs pre-operation, $P = 0.871$), 2.1370 ± 0.3865 mg/l (vs pre-operation, $P = 0.719$), respectively. The serum β_2-MG levels in the open surgery group were 2.2435 ± 0.3259 mg/l, 2.2435 ± 0.3259 mg/l (vs pre-operation, $P = 0.247$), 2.1950 ± 0.2032 mg/l (vs pre-operation, $P = 0.806$), 2.2375 ± 0.3550 mg/l (vs pre-operation, $P = 0.976$), respectively. There was no statistically significant difference between pre- and post-operation values ($P > 0.05$) in both the groups. On the same days after operation, there was no statistically significant difference between the two groups ($P = 0.410$, $P = 0.475$, $P = 0.422$, respectively) (Fig. 3).

Levels of urine β_2-MG in the PNL group on the day before operation and on the first, third and sixth days after operation were 0.2651 ± 0.0536 mg/l, 11.5695 ± 1.7451 mg/l (vs pre-operation, $P = 0.000$), 0.3180 ± 0.1445 mg/l (vs pre-operation, $P = 0.954$), 0.2508 ± 0.0495 mg/l (vs pre-operation, $P = 0.988$), respectively; there was statistically significant difference between pre- and the first day post-operative periods ($P < 0.05$); there was no statistically significant difference between pre- and the third and sixth post-operation days ($P > 0.05$). The urine β_2-MG levels in the open surgery group were 0.2788 ± 0.0859 mg/l, 28.3810 ± 2.1685 mg/l (vs pre-operation, $P = 0.000$), 4.3370 ± 0.8032 mg/l (vs pre-operation, $P = 0.040$), 0.3331 ± 0.0983 mg/l (vs pre-operation, $P = 0.978$), respectively; there was statistically significant difference between pre- and first and third day post-operation ($P < 0.05$); there was no statistically significant difference between pre- and the sixth day post-operation ($P > 0.05$). On the same days after operation,

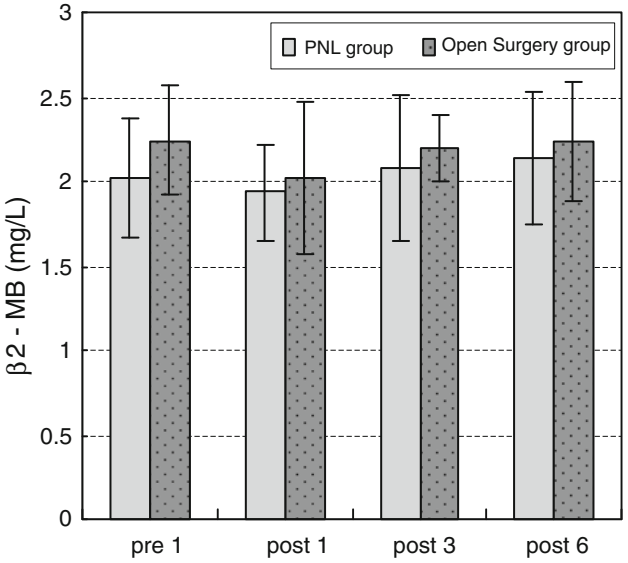

Fig. 3 Serum β2-MG in PNL and open surgery group

there was significant difference between the two groups ($P = 0.000$, $P = 0.000$, $P = 0.023$, respectively) (Fig. 4).

Discussion

At present, PNL has become the first choice of the treatment for kidney stone in a number of clinical centers [13]. The impact of PNL, as well as open surgery in patients with nephrolithotomy on the immune system, SIRS and renal function, had not been studied in detail.

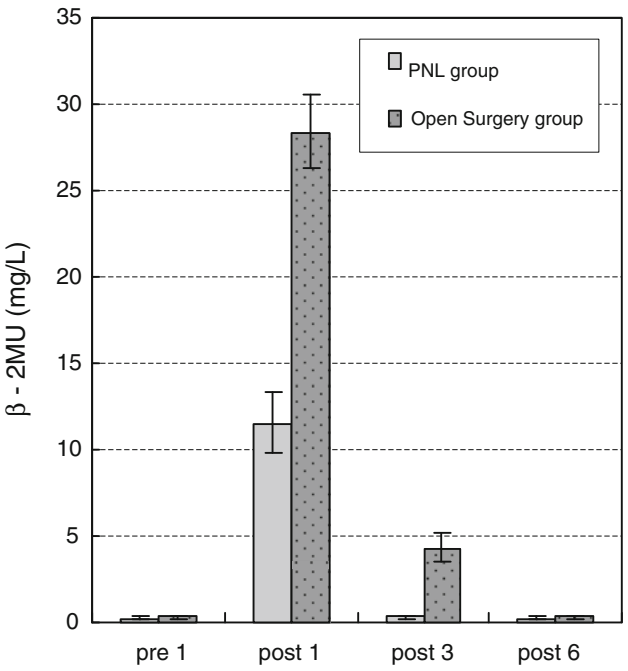

Fig. 4 Urine β2-MG in PNL and open surgery group

CRP is an acute reactive protein. As a sensitive indicator, serum CRP may dramatically increase in patients with acute inflammation, acute trauma, or infection after surgery; and its level is positively correlated with the extent of inflammatory response or tissue trauma; if severe infection is absent, it would decrease to normal shortly after operation [11].

Our study shows that in both the PNL group and the open surgery group, CRP was normal before operation. But after operation, it dramatically increased on the first day and peaked on the third day; its level gradually decreased on the sixth day, but still was higher than the preoperative levels. This suggests that the surgical patients had an acute non-specific inflammation after operation which resolved within a week. However, the serum CRP concentration of open surgery group after operation was significantly higher than that of PNL group. Since CRP correlates with the degree of trauma, PNL appears to induce less systematic stress response than open surgery.

Interleukin-6 (IL-6) is an important cytokine in stress response and immune regulation. Ischemia and reperfusion following post-traumatic inflammation can activate neutrophils, macrophages, monocytes, etc. [14]. These cells release many cytokines such as TNF-α which can further induce IL-6, IL-8 and other cytokines in a positive feedback loop. Induced by IL-6, liver cell can synthesize certain acute reactive proteins after trauma. Therefore, the level of serum IL-6 post-operatively is a sensitive marker of the degree of tissue damage [15, 16].

Serum IL-6 of PNL group and open surgery group were normal preoperatively. It peaked on the first day after operation. On the third and sixth days, IL-6 levels decreased gradually. But IL-6 in the sixth day after operation was still higher than that of pre-operation. It suggests that patients of both the groups produced high levels of inflammatory cytokines and acute non-specific inflammation. The acute non-specific inflammation gradually returned to normal after a week or so. However, IL-6 levels of open surgery group in the postoperative first, third, sixth days were significantly higher than these of PNL group. Thus, patients of open surgery group underwent a more severe acute nonspecific inflammation and resolved more slowly than those in the PNL group.

IL-6 generated locally after acute trauma can cause systemic effects on the target organs. IL-6 can stimulate liver cell to synthesize CRP which can be secreted into the blood circulation. Sustained stimulation by IL-6 can induce persistent synthesis of CRP and the level of CRP correlates with the degree of tissue damage. In this study, serum IL-6 peaked on the first day and serum CRP peaked on the third day post-operation in both the groups. Increase of IL-6 after surgical trauma occurred earlier than that of CRP. IL-6 started to decrease on the third day after operation, followed by rapid decrease of CRP level to the normal range. Therefore, serum IL-6 was an earlier and more sensitive indicator of stress reaction than CRP.

SIRS is a pathophysiologic process of infection–inflammation–grave syndrome after trauma and tissue damage. In this process, damage factors stimulate the inflammatory cells to release inflammatory factors, such as tumor necrosis factor alpha, interleukin-1, interleukin-6, nitric oxide, platelet activate factor, etc. Generally, they could contribute to restore the body as a defense mechanism after trauma. IL-6 is one of the key components. These cytokines can cause acute period of protein elevation. However, if the inflammatory reaction is excessive or the duration very long due to infection or tissue damage and so on, inflammation factors would be excessively released [9, 17]. Our study had 5 cases of SIRS in PNL group and 12 cases in open surgery group. Therefore, trauma of open surgery was more severe than that of PNL.

The diagnostic criteria of SIRS include temperature, respiration, heart rate and WBC. In our study, respiration and heart rates were abnormal in a proportion of patients but were not serious. Cases with temperature and WBC abnormality were very few. After surgery, the acceleration of respiration and heart rate is also a response to stress. The reason the number of cases of SIRS in the PNL group was smaller than that of the open surgery group may also relate to the degree of surgical trauma.

β_2-MG is the light chain protein component of histocompatibility antigen in human body cell membranes, particularly lymphocytes and tumor cell membrane. In the urine, 99.9% β_2-MG can be absorbed and decomposed in proximal renal tubules and only trace of β_2-MG is discharged in the urine [10]. Mcqueen [18] and co-workers believed that if the net absorption of β_2-MG decreased by 1%, urine β_2-MG can increase 30 times. Therefore, β_2-MG can be used as a marker of glomerular filtration and renal tubule reabsorption function.

In our study, the serum β_2-MG did not change significantly in either the PNL group or the open surgery group and hence the procedures did not have obvious effect on glomerular filtration function. In the PNL group, urine β_2-MG of the first day after surgery was significantly higher than that before operation and it decreased to normal on the third day after operation. This suggests that PNL can affect the renal tubular reabsorption function early after operation. In the open surgery group, urine β_2-MG decreased to normal on the sixth day after operation, suggesting that open surgery had more effects on renal tubular reabsorption function and it took the body longer to return to the normal state.

Conclusions

The systemic stress response is activated to some extent in both the PNL group and the open surgery group. The degree of stress response by percutaneous nephrolithotomy is lower than that of open surgery. There were different cases in both the groups with SIRS, but the degree of SIRS in PNL group is less than the open surgery group.

PNL and open surgery both have no obvious effect in glomerular filtration function after operation and both of them have effect in renal tubular reabsorption function in the early stage after operation; but the recovery of the PNL group is faster than the open surgery group. Therefore, PNL is a safe and effective procedure which causes milder degree of tissue damage and renal function abnormality.

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