Original Article

Role of Vitamin C and E supplementation in reduction of serum level of renal injury marker following shock wave lithotripsy: Prospective single centre experience

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Abstract

Introduction: Shock wave lithotripsy has become first line treatment modality for renal calculi due to its noninvasiveness. However, the destructive forces like dispersion of cavitation bubbles can cause trauma to thin-walled vessels and renal parenchyma during fragmentation of the stones. Antioxidants are our first line of defense against oxidative stress. The aim of this study was to investigate whether oral administration of Vitamin C and E help in a reduction of the serum level of inflammatory mediator by serial measurement of high sensitivity C-reactive protein (hs-CRP) and by this reduction in the risk of renal damage.

Patients and Methods: A total of 107 subjects were recruited in three groups. Group A served as a control group, and Group B and Group C received oral medication of Vitamin E 800 mg/day and Vitamin C 1000 mg/day respectively, start from 2 days prior the lithotripsy and continued for total 7 days. The level of hs-CRP was used as a mediator of the inflammatory response following lithotripsy and thus for long term renal injury. Serum level of hs-CRP was measured on 2 days prior the lithotripsy and day 2, 7 and 28 after the lithotripsy.

Results: Patients who were given either Vitamin C or Vitamin E showed a significant reduction of serum level of hs-CRP when compared to control the group.

Conclusion: Oral administration of Vitamin C and E helps in reduction of serum levels of the inflammatory marker for acute renal injury and thus they can be useful in minimizing the kidney injury following lithotripsy for renal stone disease.

Key Words: Antioxidant, C-reactive protein, inflammatory marker, lithotripsy, Vitamin C and Vitamin E

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INTRODUCTION

In 1980, Chaussy *et al.* 1st time described shock wave lithotripsy (SWL) to break up kidney stones.[1] Since then, it has revolutionized the management of stone disease. However, it is not free of complications. The destructive forces like dispersion of cavitation bubbles and shear forces can also cause trauma to thin-walled vessels in the kidneys and adjacent tissues, while fragmentation of the stones.[2] This inflammatory reaction may lead to the formation of scar and possible chronic loss of tissue function. C-reactive protein (CRP) is the most widely studied marker of systemic inflammation.[3] Recent advancement suggests that high sensitivity CRP (hs-CRP) has more accurate value than conventional CRP in the general population.[4]

Antioxidants are our first line of defense against oxidative stress and may reduce the consequences of the inflammatory process

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in the body. The aim of this study was to investigate whether oral administration of vitamins helps in reduction of the serum level of inflammatory mediator by serial measurement of hs-CRP and by this reduction in the long-term risk of renal damage. Though, Vitamin C and E are among the most extensively studied dietary antioxidants,[5] they have not been studied individually to see their role for the inflammatory process associated with SWL.

PATIENTS AND METHODS

This study was conducted between September 2012 and August 2013 at Institute of Kidney Diseases and Research Centre and Institute of Transplantation Sciences, centre. All patients with renal calculi (radio-opaque stones <1.5 cm size) and who were candidates for SWL were given option of this study. Patients between age of 18 and 50 years with solitary renal stone were included in the study. Patients with raised total leucocytes count, positive urine culture and raised serum creatinine (serum creatinine > 1.2 mg/dl) were excluded from the study. Patients with a history of previous surgical treatment for stone disease and those with any congenital renal anomaly were also excluded from the study. Total three treatment groups were made as described below and followed-up.

Standard blocked randomization method was used to select the individuals into the three treatment groups. Approval from the local ethical committee was taken prior the study, and informed consent was taken.

- Group A (n = 36): Patients in this group served as a control group and were not given any vitamins
- Group B (n = 36): Patients received oral medication of Vitamin E 800 mg/day, started 2 days prior the lithotripsy and continued up to 5 days after lithotripsy (total 7 days)
- Group C (n = 35): Patients received oral Vitamin C 1000 mg/day, started 2 days prior the lithotripsy and continued up to 5 days after lithotripsy (total 7 days)

Blood and urine samples were collected from all patients according to the following schedule

- Sample 1: 2 days prior to lithotripsy (pre litho day 2) laboratory investigations included complete blood count, serum creatinine, random blood sugar, hs-CRP and urine for microscopy with culture
- Sample 2: After 48 h of lithotripsy (day 2) serum hs-CRP was measured
- Sample 3: 7 days after lithotripsy (day 7) serum hs-CRP was measured
- Sample 4 (last sample) was taken 28 days after the lithotripsy - serum hs-CRP and serum creatinine was measured.

The whole blood was taken on each occasion and the serum was separated and analyzed in batches within 10 min of collection. Demographic data, including age, sex, height, weight, and stone size were analyzed.

Entire data submitted in excel was thoroughly evaluated using ANNOVA test and Student's *t*-test. ANNOVA test used to compare mean between three groups. Continuous variables were compared by Student's *t*-test. P <0.05 or less was considered to be statistically significant.

RESULT

Totally 107 patients were evaluated at the end of 3 months (lost to follow up, n = 7). Demographic data, including age, sex, height, weight, and stone size were comparable and there was no significant difference among them in all three groups [Table 1]. The mean stone size was 11.2 ± 2.78 cm in Group A, 12.7 ± 1.04 cm and 11.4 ± 1.78 cm, respectively in Group B and Group C.

In all three groups hs-CRP level increased on 48 h after the SWL and gradually it becomes normal to its baseline. On pre litho day (before the start of antioxidant medication) mean value of hs-CRP among three groups was not significant (ANNOVA, 0.55). However, on day 2, 7 and day 28,

Table 1: Clinical characteristics of patients

	Group A (placebo)	Group B (vitamin E)	Group C (vitamin C)
Number of patients	36	36	35
Sex			
Male	29	32	30
Female	7	4	5
Age (years)	40.5±3.78	39.5±4.98	40.3±4.21
Weight (kg)	72.3±4.67	71.6±4.98	72.5±5.56
Height (cm)	165.6±13.45	167.56±11.30	163±12.67
Creatinine (mg/dl)	0.98±0.24	0.92±0.27	0.8±0.3
Stone size (mm)	11.2±2.78	12.7±1.04	11.4±1.78
Adverse events (nausea)	1	2	1

Demographic data including age, sex, height, weight and stone size were comparable and there was no significant difference among them in all three groups

Table 2: Mean hs-CRP value in all three groups on day 0, day 2, day 7 and day 28. On day 0 mean value of hs-CRP among three groups was not significant (ANOVA, 0.55). But on day 2, 7 and 28, the values were significantly different among all three groups (ANOVA, <0.05). On further analysing results, mean hs-CRP value was significantly lower in Group B and Group C (student's *t*-test, *P*<0.05) compared to Group A (day 2, 7 and 28)

	Day 0	Day 2	Day 7	Day 28
Group A	2.59±2.28	6.01±6.42[a, b]	5.58±5.89[a, b]	4.48±4.61[a, b]
Group B	2.60±2.17	3.56±2.22[a, c]	2.69±2.26[a, c]	2.11±1.68[a, c]
Group C	3.13±2.64	3.05±3.17[b, c]	2.45±2.18[b, c]	1.52±1.07[b, c]

In Group C mean hs-CRP value was lower than Group B, but did not reach statistical significance (student's *t*-test, P>0.05). Lowest mean hs-CRP value achieved in Group C patients at day 28 (1.52). P value (student's *t*-test) - day 2: [a]0.034; [b]0.016; [c]0.433, day 7: [a]0.007; [b]0.004; [c]0.65, day 28: [a]0.005; [b]0.004; [c]0.08. hs-CRP: High sensitivity C-reactive protein

the mean value of hs-CRP was significantly different between the three groups (ANNOVA, <0.05) [Table 2]. On further analyzing results, mean hs-CR*P* value was significantly lower in Group B and Group C (Student's *t*-test, $P < 0.05$) compared to Group A on day 2, 7 and 28 after the lithotripsy [Figure 1]. In Group C mean hs-CR*P* value was lower than Group B, but did not reach statistical significance (Student's *t*-test, $P > 0.05$). Lowest mean hs-CR*P* value achieved in Group C patients at day 28 (1.52).

DISCUSSION

Shock wave lithotripsy has become the first line treatment modality for small renal calculi (<2 cm) due to its noninvasiveness and high efficacy.[6] In spite of that, it is not free from side effects. SWL may induces renal parenchymal injury and promotes further damage to kidney function in an experimental animal studies.[7] The acute vascular lesion caused by SWL can results in a loss of nephrons by scar formation. In a study on dogs, Newman *et al*. have reported this sort of chronic damage and fibrosis after 1 month of treatment with the Dornier HM-3 lithotripter.[8]

A transient decrease in renal perfusion leads activation of reactive oxygen species (ROS) in the tissue and ultimately results in functional damage which is even higher in reperfusion phase.[9]

Renal injury after ischemia-reperfusion (I/R) is mainly due to ROS.[10] An increased excretion of small molecular proteins (β2 and α1 microglobulin) and some enzymes (N-acetyl-β-glucosaminidase) and reduction in the excretion of tamm horsfall protein are markers of tubular damage.[11-13]

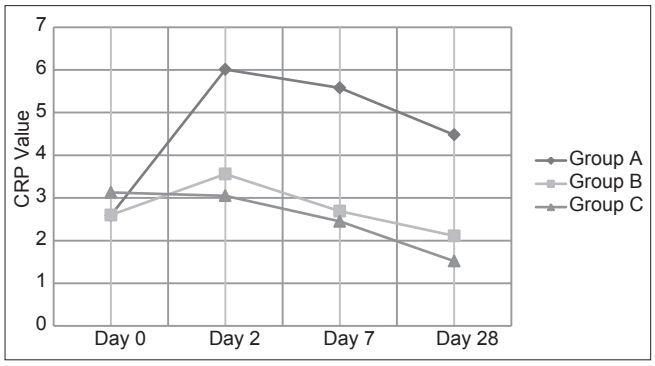

Figure 1: The graph shows mean high sensitivity C-reactive protein (hs-CRP) value increased in all three groups after 48 h of lithotripsy but then gradually it came down. The mean hs-CRP value was significantly lower in Group B (Vitamin E) and Group C (Vitamin C); (Student's *t*-test, $P < 0.05$) compared to Group A (no antioxidant) on day 2, 7 and 28 after the lithotripsy. In Group C (Vitamin C) mean hs-CRP value was lower than Group B (Vitamin E), but did not reach statistical significance (Student's *t*-test, $P > 0.05$). Lowest mean hs-CRP value achieved in Group C (Vitamin C) patients at day 28 (1.52)

C-reactive protein was first obtained as a precipitin, which forms in the serum of patients and reaches a maximal level in 2-3 days after the acute stimulus and later starts decreasing rapidly.[14] Its half-life is 16-18 h. In chronic inflammatory diseases, CRP levels may remain constantly high.[15]

What is the explanation for our results?

It has not been elucidated in details that how antioxidants work in kidneys? However, free radical formation after I/R injury following lithotripsy has been documented in multiple investigations.[16] In addition, oxidative stress also causes the generation of ROS that can ultimately lead to renal injury. Free radical species can be divided in two groups; first one is ROS and the other one is reactive nitrogen species.[17] ROS is more important, and it is mainly associated with endothelial dysfunction. When the ROS attach to cell membrane lipids, an initiation of peroxidation occurs, which can ultimately lead to alteration of cell membrane integrity, following which the cellular equilibrium is lost, and finally cell death occurs. In normal circumstances, ROS neutralized by the cellular antioxidant enzymes like superoxide dismutase, catalase, glutathione peroxidase, etc.[17] Renal injury by lithotripsy produce imbalance between normal cellular antioxidant enzyme defence system of the body and excessive free radicals. These extra free radicals ultimately lead damage to lipids, proteins enzymes and DNA.

Antioxidants give their electron to ROS and covert them to a harmless molecule. The mechanism of Vitamin C is scavenging of superoxide anion by forming semidehydroascorbate radical, which is subsequently reduced by glutathione.[17] Vitamin C is most important water-soluble antioxidant in extracellular fluids. It is capable of neutralizing ROS in the aqueous phase before lipid peroxidation starts. On the other hand, Vitamin E is a major lipid-soluble antioxidant, direct scavenging of superoxide and upregulation of antioxidant enzymes and is effective in breaking chains within the cell membrane and thus it protects membrane fatty acids from lipid peroxidation.[17] It has been cited that Vitamin C has capability of regenerating Vitamin E.[18] In one study, it has been suggested that Vitamin C also work with glutathione to reduce ROS and elevated CRP both.[19] The decrease in mean hs-CRP observed in our study indicates that Vitamin C and E minimize the renal injury following lithotripsy by scavenging free radical species in renal tissue.

In another study, authors showed that Vitamin C helps to prevent the gentamicin induced nephrotoxicity; the effect was demonstrated by nephrotoxicity indicators (serum creatinine, blood urea nitrogen, and antioxidant activity) when compared to control grou*P* values.[20]

To the best of our knowledge, only few studies have been done on the role of antioxidants in the lithotripsy related renal injury and interestingly, most of them used combination of antioxidants.[21-23] Kehinde *et al.,* have shown that oral antioxidant therapy prior to lithotripsy is associated with reduction in the serum levels of mediators (CRP and serum alkaline phosphatase) of renal injury following lithotripsy.[23] Both direct and indirect mechanisms can explain the protective effect of antioxidants against the shock wave induced tubular damage. In our study we used specific antioxidant Vitamins C and E to know the effect of each antioxidant.

Furthermore, Tungsanga *et al.,* have recently showed that the calculus state is partly brought about by excess free radicals in the circulation. Hence, the oral intake of antioxidants for long period may help in the prevention of stone recurrence.[24]

Like other studies, there were a few limitations to our study. First, our study was limited geographically to the local area and had a relatively small population. Second, the period of the study was short. Recently, Krambeck *et al.* showed that patients given SWL may have an increased risk of developing hypertension, proteinuria or diabetes mellitus >5 years after receiving the lithotripsy treatment.[25] Further studies are required to comment whether the long-term deleterious effects of lithotripsy can be avoided with the use of Vitamin C and E.

The other limitation is that there are multiple factors that can affect the levels of inflammatory markers like coronary artery disease or other systemic disease. To minimize the effect of coronary artery disease on hs-CRP, we selected age group of <50 years. In our study, we used sequential measurement of hs-CRP rather than a single value of it to eliminate the effect of another inflammatory process of the body. CRP is a more sensitive and gives a better reflection of the acute phase response than the erythrocyte sedimentation rate (ESR). hs-CRP has even more predictive value then CRP. The CRP level is mainly determined by the rate of its production (and hence the severity of the precipitating cause) due to its relatively constant half-life. In the first 24 h, ESR may be normal, and CRP elevated. CRP returns to normal more quickly than ESR in response to therapy.

CONCLUSION

Our results prove that use of Vitamin C and E as antioxidants during lithotripsy lead to a reduction in serum levels of the inflammatory marker by scavenging free radical species in renal tissue. Thus, Vitamin C and E can be useful in minimizing the kidney injury following lithotripsy for renal stone disease. However, further long-term multicentric study is needed to confirm these findings.

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