

The effect of vitamin A on renal damage following acute pyelonephritis in children

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Abstract Animal studies suggest that administration of vitamin A to rats with experimental urinary tract infection decreases the frequency of renal scars (Kavukçu et al., *BJU Int* 83(9):1055–1059, 1999). The aim of this study was to determine the effect of vitamin A on the rate of permanent renal damage in children with acute pyelonephritis. Fifty children, median age of 24 months (range 2–144), with first-time pyelonephritis verified by an uptake defect on acute dimercaptosuccinic acid (DMSA) scan were included in the study and randomly allocated to the case or control groups. All were given intravenous ceftriaxone for 10 days followed by oral cephalexin for 3 months. Cases in addition were given a single intramuscular dose of vitamin A, 25,000 U for infants below 1 year of age and 50,000 U for older children. At the repeat DMSA scan after 3 months, five of 25 cases (20%) and 17 of 25 controls (68%) had abnormal findings ($p=0.001$). In conclusion, administration

of vitamin A was associated with a significantly lower rate of permanent renal damage.

Keywords Acute pyelonephritis · Children · Renal scar · Vitamin A

Introduction

Urinary tract infection (UTI) is considered as one of the most common infections of childhood and also the most frequent infection of the urogenital system. Although UTI has a prevalence of 3–5% in girls and 1% in boys, the importance of the infection is that if not timely diagnosed, it could result in septicemia or the occurrence of long-term complications such as hypertension and even chronic renal failure [19]. These complications are mainly produced following the formation of renal scarring in patients with UTI. Renal scarring is significantly correlated with presence of gross vesicoureteral reflux and recurrent pyelonephritis [12]. According to several studies, vitamin A deficiency causes an increase in urinary infections incidence while the administration of vitamin A leads to reduction in UTI incidence [2,4,6,15]. In a study performed on children with recurrent UTI, the severity of renal scarring was revealed to have an inverse correlation with the serum vitamin A concentration [13,15]. There are several factors affecting the degree of renal tissue damage such as bacterial colonization, endotoxin production, interleukin, and oxidative effect [3,13,21].

Vitamin A is needed by all epithelial cells of body tissues. Vitamin A deficiency leads to development of keratinizing, metaplasia in the respiratory, urinary, and other organs [14]. The effect of vitamin A in infections of respiratory and digestive systems is widely investigated

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[14,16,23,25]. Based on data findings of these studies, the WHO suggests that children must have a recommended dose of vitamin A capsule every 6 months [8]. There are a limited number of studies regarding the effect of vitamin A in urinary tract infections [13,15]. On the contrary, in another study, the administration of vitamin A not only failed to considerably affect the clinical and pathophysiological course of renal ablation nephropathy in rats but also when given at higher doses it could cause damage to kidney tissue [22]. Considering the findings of different studies and since even a longer intravenous therapy was found to lack the potential of reducing the renal scar [5], the present study was attempted to investigate the effect of vitamin A on reduction of renal damage due to acute pyelonephritis and based on results of dimercaptosuccinic acid (DMSA) renal scan. DMSA renal scan is the method of choice for identification of renal lesions secondary to acute inflammation of parenchyma. The radionuclide evaluation of renal function helps to differentiate between cystitis and pyelonephritis [1].

Materials and methods

This was a prospective and interventional study performed on a population including all infants and children over 2 months with definite diagnosis of acute pyelonephritis based on DMSA scan. All children were admitted to Qazvin Children Hospital, affiliated to Qazvin University of Medical Sciences, during the winter 2006 to summer 2008. This was a randomly single-blind clinical trial in which only the clinician and the parents knew whether a patient was taking the standard treatment or the new therapeutic protocol, but the physician in charge of isotope center was unaware to which group the patient belongs. In accordance with formula for determining the sample size, a total of 50 hospitalized patients with acute pyelonephritis (for the first time) were selected. Later, the patients (50) were divided randomly into two groups of 25 members: One as control group only received antibiotic and the other marked as the case group received antibiotic plus vitamin A. Both groups were matched for age and gender. For all patients hospitalized with diagnosis of acute pyelonephritis, laboratory tests and imaging study including urinalysis, urine culture, CBC, erythrocyte sedimentation rate, C-reactive protein, sonography, voiding cystourethrography, and DMSA scan were performed. Inclusion criteria were (1) body temperature $\geq 38.5^{\circ}\text{C}$, (2) positive urine culture of a single organism $\geq 10^5$ CFU/ml obtained either by a catheter or a midstream clean-catch specimen, (3) lack of a previous history of UTI with fever, and (4) DMSA scan indicating acute pyelonephritis (reduced focal or multifocal perfusion defects on unilateral or bilateral kidneys on DMSA scan). Also, the exclusion criteria included (1)

patients with vesicoureteral reflux of a grade $> \text{III}$, (2) anatomic disorders, (3) neurogenic bladder, and (4) urinary calculi. Ceftriaxone at a dose of 75 mg/kg twice a day was administered if the acute pyelonephritis was confirmed. The dosage of vitamin A was calculated at 1,500 U/kg/day (a maximum of 50,000 U) and given as a 25,000-U single dose for infants below 1 year and 50,000 U for the infants and children over 1 year through intramuscular injection at the time of hospitalization. Antibiotic therapy with ceftriaxone continued for 10 days and followed by administration of prophylactic treatment with cephalexin syrup (15 mg/kg). A second renal DMSA scan was performed for each patient 3 months after hospital discharge, and the degree of damage and the occurrence of scar were compared with those of the first renal DMSA scan [7,12]. It is worth mentioning that between the first and the second renal DMSA scans, all patients were requested to have monthly U/A and U/C for detection of recurrent UTI although none was found to suffer any recurrent urinary tract infection. The data were analyzed using statistical chi-square and Student's *t* tests.

Ethical considerations (ethics)

All parents were given clear explanations regarding the methodology of the research and also lack of any harmful effect due to the dose of vitamin A administered. The present study was ethically confirmed by ethical committee of hospital, as the children were included in the study only if their parents were satisfied and signed the consent form.

Results

According to our findings, 42 of the patients were females and eight males. The minimum and the maximum age among two groups were 2 and 144 months with a median of 24 months. Both groups of patients were febrile and median body temperature was 39°C . Thirty-four patients out of 50 had increased peripheral WBC count. Pyuria was seen in all patients in initial urinalysis. All had positive urine cultures. *Escherichia coli* was isolated from the urine of 45 patients. There was no significant difference between the two groups associated with age and gender ($p > 0.05$). Out of 50 patients in both groups with primary abnormal renal DMSA scan, five cases of the case group and 17 in control group were still found to have an abnormal result on their second renal DMSA scan performed 3 months later following the hospital discharge. In the case group, the second renal DMSA scan revealed unilateral one focal area of diminished uptake in three patients. But two patients had two focal (unilateral) areas of diminished uptake. In the control group, the second renal DMSA scan showed one

focal area of reduced uptake unilaterally in 13 patients. On the other hand, four patients had two focal area of reduced uptake unilaterally. Statistically, a significant difference between two groups was established ($p=0.001$).

Discussion

Several studies have investigated the effect of antioxidants such as vitamin A, vitamin E, allopurinol, prednisolone, and dexamethasone on prevention or reduction in severity of renal scar formation. The majority of these studies used laboratory animal models [3,9,14,18,20], and to our knowledge, only two studies of this kind were performed on children [13,21]. There are other studies in which the effects of pentoxifylline, melatonin, and ebselen on prevention of renal scar were examined, but again all were carried out on animal models [10,11,26]. In the present study, of 25 patients with primary abnormal renal DMSA scan in the case group, only five children were demonstrated to have abnormal renal scan on their second scans 3 months after the hospital discharge. Among the control group, the results of renal DMSA scans were significantly different as shown by the second renal scans in which 17 patients were still revealed to have abnormal findings and the difference between two groups was shown to be statistically significant ($p=0.001$).

What makes the present research different from the other studies is that in our study, the beginning of the clinical trial was coincident with the appearance of the signs and symptoms of acute pyelonephritis whereas in most previous studies on animals, the antioxidant was immediately administered following the direct inoculation of bacterial suspension into the kidneys. In some other experimental studies on animals, it was reported that if the administration of antioxidants performs 72 h post-inoculation of bacterial suspension into kidney, no sign of reduction in renal scar is obvious [14,17,24]. The findings of the current study is totally different from those of earlier works as shown by the results of the second renal DMSA scans 3 months after hospital departure while vitamin A was injected as a single dose at a time the signs and symptoms of acute pyelonephritis appeared. This means that if vitamin A is even injected after the occurrence of symptoms of pyelonephritis, it still has a substantial effect in preventing renal scar ($p=0.001$).

As far as the literature is concerned, no such hypothesis is investigated in previous studies on human subjects, and there is only one study on mice in which the antioxidants were administered following a rise in body temperature, indicating that even at this stage, the application of antioxidants could diminish the renal injuries and prevent the long-term complications of pyelonephritis [20]. In another study by Soyly et al. on Wistar rats, it was found that the administration of vitamin A or the serum level of

this vitamin is of no considerable effect on the course of renal ablation nephropathy in mice undergone subtotal nephrectomy [22]. It can be concluded that the authors suggested further investigations on advantages and toxic effects of vitamin A on kidney tissues. Bouissou et al. in their study reported that even the long-term administration of intravenous antibiotic failed to prevent the formation of kidney scars in all children with acute pyelonephritis [5]. Considering the side effects and extra cost of long-term intravenous antibiotic treatment and also the lack of preventive effect on formation of kidney scar, the value of vitamin A in preventing kidney scar formation, once again, is demonstrated. Also, in a study by Sharifian et al., it was concluded that the administration of dexamethasone could possibly prevent the formation of kidney scar [21]. Regarding this and comparing the side effects of dexamethasone and vitamin A, again the beneficial effects of vitamin A make this chemical as a valuable drug in treatment of acute pyelonephritis and eventually in prevention of kidney scar formation. Although the low number of patients may be considered as the limitation of the current study, however, by increasing the number of patients in future studies, the accuracy and reliability of the present results can be increased too.

Conclusion

To our knowledge, this is the first research associated with the effect of vitamin A on pyelonephritis in children in which the injection of vitamin A is performed at a time when the patient demonstrates all clinical and laboratory findings, with results of renal DMSA scan also available. The present study shows that even the febrile children with pyelonephritis, on admission to the hospital, still could benefit the useful effects of vitamin A in preventing kidney scar. This research could be regarded as a basis for further large-scale studies in which the comparison of different antioxidants should also be targeted.

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Conflict of interest There is no conflict of interest (we did not have any financial relationship).

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