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Review Article

Use of antioxidants in urinary tract infection

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ABSTRACT

Pyelonephritis is an inflammatory process, and oxidative stress plays a major role in it. Anti-inflammatory or antioxidant therapy given concomitantly with antibiotics should lower the risk of postpyelonephritic scarring. As the lack of review studies in the use of antioxidants in urinary tract infections was detected, this study was designed. We conducted a review of available articles in PubMed and Google Scholar with a simple review, using keywords of "antioxidant" and "pyelonephritis" with all their possible synonyms and combinations. Only interventional studies were collected. There were neither limitations on time, nor the location of the study, type of subjects, administration rout of the antioxidant drug, and the antioxidant drug used. After studying the abstracts or in some cases the full text of articles, they were categorized based on the type of antioxidant, type and number of subjects, rout of administration, dosing, duration of treatment, year of publication of the paper, and the results. A total of 66 articles published from 1991 to 2015 were found by studying just the title of the papers. Studying the abstracts reduced this number to 51 studies. Antioxidants used for this condition were Vitamins A, E, and C, cytoflavin, caffeic acid phenethyl ester, ebselen, allopurinol, melatonin, N-acetylcysteine, oleuropein, montelukast, oxytocin, ozon, dapsone, pentoxifyllin, tadalafil, bilirubin, cranberry, meloxicam, L-carnitine, colchicine, perfluoran, methylprednisolone, and dexamethasone. Studies show that antioxidants are capable of reducing oxidative stress and can be used effectively along with antibiotics to reduce the scar formation.

Keywords: Antioxidant; pyelonephritis; urinary tract infection

INTRODUCTION

Although oxidation reactions are crucial for life, they can also damage cells. Cells contain a complex network of antioxidant systems to prevent oxidative damage to cellular components. In general, antioxidant systems either prevent reactive species from being formed or remove them before they can damage vital components of the cell. When antioxidant defense mechanisms are decreased, or when the generation of reactive oxygen molecules is increased, oxidant injury results from the shift in the oxidant/antioxidant balance.

Oxidative stress seems to play a significant role in many human diseases including cancers and infections. Several renal diseases including glomerulonephritis, vasculitis, toxic nephropathies, pyelonephritis, acute renal failure, and others are likely to be mediated at least in part by oxidant injury.

Pyelonephritis is an inflammatory process, and oxidative stress plays a major role in it. According to the results of a study, the concentration of biomarkers of oxidative stress was markedly increased in the blood and urine of children with kidney diseases including glomerulonephritis, pyelonephritis, renal

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failure, and lower urinary tract infections. These results suggest antioxidant therapy as a valuable option for children with kidney problems.[1]

In addition, it has been shown that in pyelonephritis (upper urinary tract infection), an infection-induced intoxication and oxidative stress can lead to cell death, and pyelonephritis can be treated by reducing mitochondrial reactive oxygen species, and thus by protecting the mitochondrial integrity and lowering kidney damage.[2]

In many studies, impaired balance between oxidant systems and antioxidant defense in patients with acute or chronic pyelonephritis is established, and some studies have declared this in the pathogenesis of tissue injury in this infection.[3-5] It seems logical that anti-inflammatory or antioxidant therapy given concomitantly with antibiotics should lower the risk of postpyelonephritic scarring.[6]

METHODS

We conducted a review of available articles in PubMed and Google Scholar, using keywords of "antioxidant" and "pyelonephritis" with all their possible synonyms and combinations. Studies showed that antioxidants are capable of reducing oxidative stress and can be used effectively along with antibiotics to reduce the scar formation.

Only interventional studies were collected. There were neither limitations on time nor the location of the study, type of subjects, administration rout of the antioxidant drug, and the antioxidant drug used. After studying the abstracts or in some cases the full text of articles, they were categorized based on the type of antioxidant, type and number of subjects, rout of administration, dosing, duration of treatment, year of publication of the paper, and results (whether the antioxidant drug was effective in reducing oxidative stress or not). We found 66 articles published from the years 1991 to 2015 by studying just the titles of papers. Studying these abstracts reduced this number to 51 studies.

VITAMINS

Vitamin A was studied as a valuable antioxidant for pyelonephritis in 3 articles. The role of Vitamin A in preventing renal scaring after acute pyelonephritis (APN) in children was established. This clinical trial study was conducted in children with APN in Mofid Children Hospital (Tehran, Iran). The patients were randomly divided into 2 groups to receive ceftriaxone and Vitamin A or ceftriaxone only. Dimercaptosuccinic acid (DMSA) renal scintigraphy was performed before the start of the treatment and 6 months later. Results were compared for renal scaring between the groups. The second DMSA scan showed a significant change in the progression of kidney injury and scaring in favor of Vitamin A administration ($P < 0.001$).[7]

In a study on 50 children with APN, all subjects 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 at the repeat DMSA scan after 3 months, 5 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.[8]

The effects of oral Vitamin A or E supplementation in combination with antibiotics for the prevention of renal scarring in APN in children were the subject of another study. This simple nonblinded, randomized, clinical trial was conducted on 61 children aged 1 month–10 years. Each patient was evaluated twice by 99mTc-DMSA scintigraphy performed at least 6 months apart. A worsening of lesions, based on the second 99mTc-DMSA scan, was observed in 42.5%, 0%, and 23.3% of the control, Vitamin E, and Vitamin A patients, respectively ($P < 0.001$). Hence, Vitamin A or E supplements were effective in reducing renal scarring secondary to APN.[9] Vitamin E was administered as an antioxidant to prevent renal scarring in APN in 4 studies, 3 studies on rats, and 1 on humans (children with APN).

In the first study on rats, all rats in Groups 1–3 were given once-daily intraperitoneal injections of ceftriaxone for 5 consecutive days, beginning on the 3rd day after inoculation. The rats in Group 2 were given allopurinol co-treatment; whereas, in Group 3, Vitamin E co-treatment was started at fever onset. Both kidneys were excised 6 weeks later, for the evaluation of histopathologic changes, apoptotic damage, and concentrations of transforming growth factor-beta (TGF-beta). Only minimal changes were found in control samples. Pathologic scores of inflammation and fibrosis in Group 1 were higher than in the Vitamin E and allopurinol groups ($P < 0.05$). Apoptosis index was also decreased in Groups 2 and 3 compared to Group 1 ($P < 0.05$). There was no significant difference in average TGF-beta levels between the study groups.[10]

The effects of co-supplementation of Vitamins E and C for preventing renal scarring in APN in rats were investigated in another study. In this study, the group which received gentamicin only had moderate to severe scaring, but the 2 groups which received Vitamin C and Vitamin E showed no or mild renal

scaring. The study showed that administration of antioxidants can protect scaring due to pyelonephritis with or without antibiotic administration.[11]

In another study, the effects of Vitamin E supplementation in combination with antibiotics for the treatment of girls with APN were investigated. In this double-blinded, randomized, controlled trial that was conducted on 152 girls aged 5–12 years with a first APN, the patients were randomized to receive a 14-day treatment with only antibiotics (control group; n = 76) and 14-day treatment with supplements of Vitamin E (intervention group; n = 76). Patients' clinical symptoms were monitored for 14 days, and urine culture was performed 3–4 days and 7–10 days after the start of the treatment and its completion, respectively. All of the girls once underwent DMSA scan 4–6 months after the treatment. During the follow-up days, the mean frequency of fever (P = 0.01), urinary frequency (P = 0.001), urgency (P = 0.003), dribbling (P = 0.001), and urinary incontinence (P = 0.006) were significantly lower in the intervention group compared to the control group. There was no significant difference in the results of urine culture 3–4 days after starting the treatment (P = 0.16) and 7–10 days after its termination (P = 0.37). There was also no significant difference between the results of DMSA scan 4–6 months after starting the treatment (P = 0.31).[12]

CYTOFLAVIN

It has been shown in a study that the antioxidant drug cytoflavin in combination with basic therapy reduces the intensity of lipid peroxidation processes with retention of the antioxidant status in patients with chronic pyelonephritis. The proposed treatment normalizes the ratio of blood plasma phospholipid fractions and erythrocytes membranes.[13]

CAFFEIC ACID PHENETHYL ESTER

Caffeic acid phenethyl ester (CAPE), an active component of propolis from honeybee hives, has antioxidant, anti-inflammatory, and antibacterial properties. The efficiency of CAPE administration in preventing oxidative damage in pyelonephritis caused by *Escherichia coli* in rats was investigated. CAPE administration reduced malondialdehyde (MDA) and nitric oxide (NO) levels, as well as xanthine oxidase activity although it increased superoxide dismutase (SOD) and glutathione peroxidase activities. Histopathological examination showed that CAPE reduced the inflammation grade-induced by *E. coli*.[14]

MELATONIN

Melatonin is a powerful antioxidant. In a study on rats, melatonin was given by intraperitoneal injection for 5 days alone or combined with the antibiotic ceftriaxone. Melatonin only and antibiotic plus melatonin treatment caused a marked reduction in the mean MDA values compared with no treatment and antibiotic-only treatment, with no significant difference compared with that of the control group. No significant differences were found in the renal scarring scores in rats receiving no treatment, and those treated only with antibiotic or melatonin. The authors concluded that when combined with antibiotics, melatonin prevents renal scar formation.[15] For reviewing the results of another study that used melatonin, please refer to the "cranberry" section.[16]

N-ACETYLCYSTEINE

N-acetylcysteine (NAC) is a potent antioxidant that has been shown in many studies to reduce oxidative stress in different conditions.[17-21] In an investigation, the contribution of free radicals to the development of APN induced by planktonic and biofilm cells of *Pseudomonas aeruginosa* was studied. Evaluation of the data revealed that excessive production of free radicals causes tissue damage, leading to bacterial persistence in the host's tissues. Treatment of mice with NAC, a potent antioxidant, lead to significant amelioration of oxidative stress and subsequent decrease in bacterial titer, neutrophil influx, MDA as well as tissue pathology highlighting the important role of free radicals in *P. aeruginosa*-induced pyelonephritis.[4]

OLEUROPEIN

Oleuropein, a novel immunomodulator derived from olive tree, was assessed *in vitro* and in experimental sepsis by *P. aeruginosa*. After addition in monocyte and neutrophil cultures, MDA, tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, and bacterial counts were estimated in supernatants. APN was induced in 70 rabbits after inoculation of the pathogen in the renal pelvis. Intravenous oleuropein prolonged survival in experimental sepsis, probably by promoting phagocytosis or inhibiting biosynthesis of proinflammatory cytokines.[22]

MONTELUKAST

One study aimed to investigate the possible protective effect of montelukast, a selective antagonist of cysteinyl leukotriene receptor 1, against *E. coli*-induced oxidative injury and scarring in renal tissue.

Pyelonephritic rats were treated with either saline or montelukast immediately after surgery and at daily intervals. It seems likely that montelukast protects kidney tissue by inhibiting neutrophil infiltration, balancing oxidant-antioxidant status, and regulating the generation of inflammatory mediators.[23]

OXYTOCIN

The neurohypophyseal hormone oxytocin facilitates wound healing and is involved in the modulation of immune and inflammatory processes. Another study investigated the possible therapeutic effects of oxytocin against *E. coli*-induced pyelonephritis in rats both in the acute and chronic setting. All inflammatory parameters and elevation of lactate dehydrogenase in the late phase were reversed to normal levels by oxytocin treatment.[24]

OZONE

One study was conducted to evaluate the effect of ozone therapy (OT), as an immunomodulator and antioxidant, on the renal function, morphology, and biochemical parameters of oxidative stress in an experimental model of APN in rats. In the abstract of this article, it has not been mentioned how ozone was given to rats. Either antibiotherapy or OT markedly ameliorated renal dysfunction, the antioxidant status of the kidneys and histopathological injuries subjected to *E. coli*-induced APN. Interestingly, the combination of antibiotherapy and OT was much more effective than either of the treatment modalities alone.[25]

PENTOXIFYLLINE

One study designed to evaluate the efficiency of pentoxifylline (PTX), a methylxanthine derivative, in preventing renal scar formation after the induction of pyelonephritis in an experimental rat model with delayed antimicrobial therapy. In this study, delayed treatment with antibiotics had no effect on scarring compared with the untreated controls. However, the addition of PTX to the delayed antibiotic therapy significantly inhibited renal scarring compared with the untreated or antibiotic-only groups ($P < 0.05$).[26]

TADALAFIL

In order to evaluate the effects of tadalafil, a phosphodiesterase 5 enzyme inhibitor, on *E. coli*-induced renal damage in an APN rat model, another study designed. Tadalafil was administered between days 0 and 28 of bacterial inoculation. Inflammatory activity was significantly milder in rats treated with antibiotic + tadalafil versus no treatment group both in the early and late periods. In the late period, interstitial fibrosis or tubular atrophy was lower in the antibiotic + tadalafil group versus the no treatment and antibiotic groups, and in tadalafil versus antibiotic group. Tadalafil administration significantly reduced renal MDA and NO levels and enhanced SOD and catalase activities. In addition, circulating TNF-α, IL 1β was greatly reduced in tadalafil group versus the no treatment group.[27]

BILIRUBIN

Protective effects of bilirubin were investigated in an experimental rat model of pyelonephritis. Inflammatory activity was significantly lower in rats treated with antibiotic + bilirubin versus no treatment group both in the early and late periods. MDA levels were significantly lower in the antibiotic + bilirubin versus the no treatment group and SOD activity was significantly higher in the antibiotic and antibiotic + bilirubin groups versus the no treatment group. When used alone, bilirubin may also prevent inflammation (in the late period) and apoptosis.[28]

CRANBERRY

Cranberry as a known antioxidant was investigated in one of the studies. One study was done to evaluate the protective effects of cranberry fruit, on infection-induced oxidative renal damage in a rabbit model of vesico-ureteric reflux. This study shows that cranberries have an anti-inflammatory effect through their antioxidant function and might prevent infection-induced oxidative renal damage.[16]

MELOXICAM AND L-CARNITINE

One study designed to investigate the involvement of oxidative stress in the pathogenesis of APN and to evaluate the impact of meloxicam and/or L-carnitine in addition to conventional antibiotic treatment. Interstitial fibrosis ($P = 0.06$), chronic inflammation ($P = 0.536$), and tubular atrophy ($P = 0.094$) decreased in group (L-carnitine and meloxicam) compared with the other groups, but there was a statistically significant decrease only in acute inflammation ($P = 0.015$).[29]

PERFLUORON

Correlation between oxygen unbalance, development of cell membrane pathology and pyelo inflammatory affection of the kidneys was studied in 67 patients with acute obstructive pyelonephritis complicated by urosepsis. It was found that surgical manipulations are

accompanied by development of reperfusion syndrome of the affected and contralateral kidney. Use of perfluoron in this situation promotes rapid compensation of gas transport disturbances, stabilization of the equilibrium in the system pro-oxidants-antioxidants, regress of pyelo inflammatory reactions, earlier recovery of functions of a more affected kidney, and anti-ischemic protection of the contralateral organ. Anti-ischemic and membrane-stabilizing actions of perfluoron make this drug adequate for use in patients with complicated renal infection.[30]

METHYLPREDNISOLONE

One study was designed to determine if adjunctive oral methylprednisolone (MPD) can prevent the renal scar formation after APN in pediatric patients. In this study, renal scarring was found in 33.3% of children treated with MPD and in 60.0% of those who received placebo ($P = 0.05$). The median cortical defect volumes on follow-up DMSA were 0.0 mL (range: 0–4.5 mL) and 1.5 mL (range: 0–14.8 mL) for the MPD and placebo groups, respectively ($P = 0.01$). Patients in the MPD group experienced faster defervescence after treatment than the placebo group.[31]

DEXAMETHASONE

A study in Iran investigated the role of dexamethasone combined with antibiotics in diminishing urinary IL-6 (UIL-6) and UIL-8 concentrations during the acute phase of pyelonephritis compared with standard

Table 1: Summary of studies of using antioxidants in pyelonephritis

Antioxidant	Type and number of subjects	Rout of administration	Dosing	Duration of treatment	Effective in reducing oxidative stress	Year of publication	Reference number
Vitamin A	Human (children) - 76	IM	25,000 IU → younger than 1-year-old 50,000 IU → 1 year or higher	Once	Yes	2011	[7]
Vitamin A	Human (children) - 50	IM	25,000 IU → younger than 1-year-old 50,000 IU → 1 year or higher	Once	Yes	2011	[8]
Vitamin A or Vitamin E	Human (children) - 61	PO	Vitamin A (1500 IU/kg/day); or Vitamin E (20 IU/day)	10 days	Yes	2012	[9]
Vitamin E or allopurinol	Rat - 20				Yes	2008	[10]
Vitamin E and Vitamin C	Rat - 60				Yes	2010	[11]
Vitamin E	Human - 152	PO	100 IU of oral Vitamin E on a daily basis, 1 tablet, daily	14 days	No	2015	[12]
Cytoflavin	Human				Yes	2011	[13]
Caffeic acid phenethyl ester	Rat - 35				Yes	2007	[14]
Melatonin	Rat	IP	20 mg/kg, once daily	5 days	Yes	2006	[15]
Acetylcysteine	Mouse				Yes	2008	[4]
Oleuropein	Rabbit - 70	IV			Yes	2006	[22]
Montelukast	Rat		Immediately after surgery and at daily intervals		Yes	2007	[23]
Oxytocin	Rat - 24		Immediately after surgery and at daily intervals		Yes	2006	[24]
Ozon	Rat				Yes	2011	[25]
Pentoxifyllin	Rat - 40	IP	50 mg/kg	5 days	Yes	2003	[26]
Tadalafil	Rat - 32				Yes	2014	[27]
Bilirubin	Rat - 32				Yes	2012	[28]
Cranberry fruit or melatonin	Rabbit - 36	PO	Feeding		Yes	2007	[16]
Meloxicam or L-carnitine	Rat - 48	IM	L-carnitine (500 mg/kg, IM) Meloxicam (3 mg/kg, IM)		Yes	2010	[29]
Perfluoran	Human - 67				Yes	2004	[30]
Methylprednisolone	Human (children) - 84	PO	1.6 mg/kg per day	3 days	Yes	2012	[31]
Dexamethasone	Human (children) - 54		0.15 mg/kg, every 6 h	3 days	Yes	2008	[32]

IU=International unit, IM=Intramuscularly, IV=Intravenously, IP=Intraperitoneally, PO=Periorally

antibiotic therapy. UIL-6 and UIL-8 concentrations were determined by enzyme immunoassay in 34 children with pyelonephritis, who were treated with ceftriaxone and dexamethasone (case group), and in 20 patients with the same diagnosis treated with ceftriaxone alone (control group). Differences between cytokine/creatinine ratios in initial and follow-up urine samples were significant in the case group ($P < 0.001$) but not for controls. In addition, combined antibiotic and dexamethasone significantly decreased UIL-6 and UIL-8 concentrations compared with antibiotic alone ($P < 0.05$).[32]

A summary of studies of using antioxidants in pyelonephritis is presented in Table 1.

AUTHORS' CONTRIBUTION

Information gathering was done by Allameh, Z. Writing and editing the manuscript was done by Allameh, Z and Salamzadeh, J.

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Conflicts of interest

There are no conflicts of interest.

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