

Effect of *Echinacea purpurea* extract on gentamicin-induced nephrotoxicity in sheep

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Abstract

Gentamicin is widely administered in small ruminant's respiratory infections. *Echinacea purpurea* [purple coneflower] has anti-inflammatory and antioxidant effects. The aim of current study was to evaluate *Echinacea purpurea* effects in gentamicin-induced nephrotoxicity in sheep. Sixteen one to two years old healthy Ghezel breed rams were selected. Gentamicin was administered 4mg/kg every 12 hours/ 10 days. In group1 concurrently, *E. purpurea* administered orally until seven days after last injection of gentamicin, and the other groups was as control. Blood and urine samples were taken to evaluate urinary casts and renal functions at day zero, ten and seventeen. Serum creatinine, urea, uric acid, and BUN were evaluated, and in urine, GGT enzyme, casts and urine was analyzed. Creatinine, uric acid, BUN, urea, and GGT decreased significantly in *E. purpurea* administered group at day ten and seventeen. Epithelial cells at day 10 and red blood cells at day 17 was seen in control group and there were absent in *E. purpurea* administered group. *E. purpurea* significantly decreased gentamicin-induced nephrotoxicity, and its adverse effects on renal function. Co-administration of *E. purpurea* and gentamicin is beneficial in sheep.

Keyword: Gentamicin; *Echinacea purpurea*; nephrotoxicity; sheep

Introduction

Infectious diseases, causes most economical losses and mortality in livestock. Due to keep flocks of sheep and heavy density of them, almost the recognition of the disease always will be done with delay. Because of fever existence in infectious disease, dehydration and loss of body water will decrease appetite and enteritis will be seen (Constable *et al.*, 2017). During dehydration, administration of antibiotics or any drugs affects kidney tissue and in severe dehydration cases there is damage in kidney tissue. In such times if administrated drug has nephrotoxicity side effects, renal function influenced and tissue injuries in kidney will increase. Gentamicin widely used in treatment infectious diseases of sheep and has nephrotoxicity effects, and even in healthy sheep in long period or high doses increase kidney toxicity. Gentamicin is an aminoglycoside antibiotic and specially used in aerobic gram-negative bacteria infection treatment (Tavafi, 2012). It is believe that the nephrotoxicity of gentamicin is because of reactive oxygen species (ROS) generation (Rafieian-Kopaei and Baradaran, 2013; Tavafi, 2012). Following ROS generation, glomerular filtration decrease and vasoconstriction increase. Gentamicin also mostly excreted in urine and accumulation in renal cortex, leads to increase damages in renal cells (Assadi, 2012). Therefore, herbal drugs with antioxidant activity, ROS scavengers should decrease the nephrotoxicity of gentamicin (Nasri *et al.*, 2013).

Echinacea purpurea [purple coneflower] is a native medicine in some parts of world include America and Europe and in Iran. It used in traditional medicine for its anti-inflammatory, anti-oxidant, anti-bacteria, and immune modulatory effects (Aarland *et al.*, 2017). *E. purpurea* also was used as food supplements in human and animals because of low toxicity and fewer side effects (Ayrle *et al.*, 2016; Chen *et al.*, 2014). *E. purpurea* decrease liver enzymes and has anti-inflammatory effects on liver and kidney (Bayramoglu *et al.*, 2011). Researchers indicated that the antioxidant properties of *E. purpurea* has reduces drug toxicity in liver (AH, 2008; Rezaie *et al.*, 2013). *E. purpurea* has free radical scavenging properties and prevent free radicals side effects in tissues (Pellati *et al.*, 2005). The aim of current study was to investigate protective effects of *Echinacea purpurea* in gentamicin induced nephrotoxicity.

Materials and Methods

Sixteen ghezel breed rams between one and two years old selected in the fall and after confirming the general health of the animals by rectal temperature, and examination of the body. All animals, which was appear healthy, with no history of disease in recent months, selected for study. The study was conducted in one of the semi-industrial livestock of Azarshahr city from Tabriz environs.

Rams selected and isolated, then health of renal functions was confirmed. To evaluate nephrotoxic effects of gentamicin (Abureyhan, Co), to all sixteen cases, it was administrated 4 mg/ Kg every 12 hours for 10 days (Fartashvand *et al.*, 2012). In group 1, along with gentamicin administration, daily 4 mg *Echinacea purpurea* (standard tablets, Goldaru, Co) (Kumar and Ramaiah, 2011) was given orally until seven days after last injection of gentamicin.

Second group was kept as control group to detect the nephrotoxic changes due to gentamicin. All cases was in same nutrition condition and fed with alfalfa, and concentrate. They have free access to water, ventilation and suitable bed. During the study, there were no unexpected or possible losses.

Upon completion of the study, urine sampled by respiratory arrest and blood samples was taken to evaluate renal function, casts and urinary sediment at day zero, tenth and seventeenth, respectively. Samples, was sent to a medical laboratory in dry ice, and the results were compared. Serum creatinine, urea, uric acid, BUN measured. The urine sediment, casts, and GGT enzyme and urine test was conducted. Dipstick test performed on the samples livestock. During the investigation, there was no illness or unpredictable circumstances, anorexia or mortality. In the control group at the end days, loss of appetite and abdominal pain was in some rams and recovered by serum therapy after completion of the research.

Independent t test was used to compare two groups at 95 percent probability levels. Data was analyzed by IBM SPSS version 22.0.

Results

Results of study indicate that at day zero there was no differences between groups in all parameters of study ($p > 0.05$). Creatinine, uric acid, BUN, and GGT was increased significantly at 10th and 17th day of study in control group ($p < 0.01$, Table1). According to results, *Echinacea purpurea* administration in group 1 successfully decreases the adverse effects of gentamicin.

Results demonstrate that there was no significance different between groups at day 10 and 17 of study in case of urinary casts, but at day 10 there was epithelial cells in urinary in 3 samples of control group, but all samples of treated group was normal. At day 17 of study red blood cells was exist in samples of control group and it was not in group 1 samples. Urinary strip test indicate in day 17, in two samples from control group was positive in case of hemoglobin. All samples of group 1 were normal in urinary strip.

Table1: Serum creatinine, urea, uric acid, BUN, and GGT in urine during various times of study (Mean±SE)

Days	Group	Creatinine (mg/dl)	Uric acid (mg/dl)	BUN (mg/dl)	Urea (mg/dl)	GGT (IU/l)
Zero	1	1.11±0.005	0.47±0.006	19.12±0.12	40.83±0.28	18.00±0.38
	2	1.11±0.005	0.47±0.006	19.12±0.12	40.83±0.28	18.00±0.38
	P value	1.00	1.00	1.00	1.00	1.00
10	1	2.02±0.07	1.01±0.08	27.00±0.32	57.96±0.53	21.50±0.90
	2	3.90±0.04	1.76±0.02	48.25±0.70	103.12±1.57	37.37±1.62
	P value	0.001	0.001	0.001	0.001	0.001
17	1	3.50±0.02	0.81±0.02	25.62±0.41	54.87±1.03	21.62±0.56
	2	6.30±0.03	2.26±0.02	58±87±0.61	126.76±0.85	49.25±1.31
	P value	0.001	0.001	0.001	0.001	0.001

Table2: The Urinary cast and urinary strip test results in different stages of study

Days	Group	Urinary cast			Urinary strip	
		Normal	Epithelial cells	RBC	Normal	hemoglobin
10	1	8	0	0	8	0
	2	5	3	0	8	0
	P value	0.055			1.00	
17	1	4	4	0	8	0
	2	2	4	2	6	2
	P value	0.264			0.131	

Discussion

The results of current research demonstrated that the *E. purpurea* co-administration with gentamicin could ameliorate the gentamicin effects on creatinine, uric acid, BUN, urea and GGT. In addition, it was indicated that the red blood cells and hemoglobin was not seen in *E. purpurea* treated group while it was seen in gentamicin control group. Results showed that the *E. purpurea* could decrease the nephrotoxicity and side effects of gentamicin in sheep.

The gentamicin is an aminoglycoside antibiotics that is administer widely in small ruminants diseases. Due to renal damages which is causes by gentamicin, its uses always will be carefully, because it could be concentrate in epithelial tubular cells and causes loss of brush borders and finally tubular necrosis, apoptosis and proteolysis will be seen in renal tissue. Some herbals relieve nephrotoxicity of gentamicin. It was reported that the garlic could ameliorate the gentamicin induced toxicity (Nasri *et al.*, 2013).

E. purpurea is commonly used herbal and has various medical properties. *E. purpurea* used in infectious disease of lower and upper respiratory system (Grimm and Muller, 1999). It was used for treatment of bowl pain, skin disorders, and chronic arthritis 3. Alkamides and polysaccharides of Echinacea extracts has immunomodulatory and anti-inflammatory properties, respectively (Gertsch *et al.*, 2004). Cichoric acid which is exist in extracts of flower prevents human cancer lines and decrease apoptosis (Tsai *et al.*, 2012). Cichoric acid contents of Echinacea has free radical scavenging activity and the antioxidant effects was because of that (Thygesen *et al.*, 2007; Tsai *et al.*, 2012). Alkamides has no antioxidant effects and only increase the cichoric acid efficacy (Thygesen *et al.*, 2007). Recent studies on rats indicated that the Echinacea has decrease nephrotoxicity and hepatotoxicity in ischemia/reperfusion injury, (Bayramoglu *et al.*, 2011). Superoxide dismutase activity, catalase and malondialdehyde levels decreased both in liver and kidney in Echinacea treated group. Damages during ischemia/reperfusion was improved in Echinacea administered groups and the histopathology changes was lower (Bayramoglu *et al.*, 2011). Researchers reported following oxidative stress, there were increase in lipid peroxidation and increase in MDA levels (Thiemermann *et al.*, 2003). The results of current study indicated that the Echinacea decrease creatinine, uric acid, BUN, GGT, and urea in treated group, and prevent hemoglobin and red blood cells excretion in urine samples. The results demonstrate Echinacea could ameliorate the gentamicin nephrotoxicity, and it was in agreement with previous studies.

Polyphenolic compounds has decrease renal dysfunction and improve kidney tissue, also they were lower lipid peroxidation and ROS in nephrotoxicity (Wongmekiat *et al.*, 2008). Findings suggest antioxidant activity of Echinacea has nephron-protective effects. Although the exact mechanism of nephrotoxicity induced by gentamicin was unknown, but oxidative and nitrosative stress has important role in this process (Cuzzocrea *et al.*, 2002).

Conclusion- The present research indicate that the co-administration of Echinacea purpurea reduces the adverse effects of gentamicin on kidney enzymes and tissue. It was shown that there was no hemoglobin and red blood cells in urine samples of co-administered groups. This study suggests that the Echinacea purpurea could be used simultaneously with gentamicin to reduce the nephrotoxic effects successfully.

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