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Effect of atorvastatin on pro-inflammatory cytokines during cisplatin administration; a double-blind clinical trial study

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ABSTRACT

Introduction: The primary concern in maintaining treatment with cisplatin pertains to the occurrence of cisplatin-induced nephrotoxicity. After the administration of cisplatin, the prospective evaluation of the effects of Atorvastatin on kidney function and inflammatory mediators was conducted.

Objectives: This double-blind clinical trial study was conducted in order to assess the changes in serum levels of tumor necrosis factor alpha (TNF-α)and interleukin-17A (IL-17A) after cisplatin administration and to ascertain the protective effects of atorvastatin against cisplatin nephrotoxicity due to the effect on the levels of cytokines.

Patients and Methods: In this double-blind clinical trial study, 30 potential candidates for the administration of cisplatin were enrolled. Patients were subsequently categorized into two distinct groups. Group A received 40 mg/d of atorvastatin on the first day of cisplatin and continued for seven days. Group B was provided with a placebo. Following the administration of cisplatin, blood samples were collected for BUN, serum creatinine, magnesium, potassium, TNF-α, and IL-17A on days 0, 8 and 21.

Results: Although there was no statistically significant difference in terms of serum urea, creatinine and glomerular filtration rate (GFR) between the two groups; however, within intra-group analysis, atorvastatin caused slower reduction of GFR compared to baseline. Though, no correlation was observed between the level of inflammatory cytokines including TNF-α and IL-17A and atorvastatin administration.

Conclusion: Atorvastatin may have the ability to prevent cisplatin nephrotoxicity; however, it does not have any effect on inflammatory cytokines.

Trial Registration: The trial protocol was approved by the Iranian Registry of Clinical Trial (identifier: IRCT20140605017982N2; https://en.irct.ir/trial/47349, ethical code: IR.SUMS.MED.REC.1398.024).

Implication for health policy/practice/research/medical education:
The nephrotoxicity of cisplatin is a significant constraint on the use of drugs. With effective preventive measures, oncologists should be able to use the drug safely. By prescribing atorvastatin before cisplatin, a smaller drop-in glomerular filtration rate occurs, which seems can be used to prevent kidney injury by cisplatin, although no significant relationship was found with the level of inflammatory cytokines, which may be due to a different mechanism of atorvastatin.

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Clinical Trial

Introduction

Cisplatin is a potent chemotherapeutic agent that inhibits the growth of cancer cells by interfering with DNA synthesis and impairing cell division (1). It is widely administered for treatment of various types of solid tumors and hematologic malignancies (2,3). The clinical effect of the drug is limited by the development of nephrotoxicity, which occurs in 30% to 40% of patients (4-6). It is a phenomenon that is influenced both by dose and duration. Repeated episodes of acute kidney injury may result in chronic kidney disease (7,8). It has been reported that inflammation, oxidative stress, apoptosis,

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and vascular injury are possible mechanisms of cisplatin nephrotoxicity (4,7,8). Immune cell infiltration into the renal parenchymal, pro-inflammatory cytokines and chemokines has been documented in the pathogenesis of cisplatin nephrotoxicity (9-12). The transcription factor tumor necrosis factor alpha (TNF-α) plays a pivotal role in the inflammatory response induced by cisplatin (6,13-15). After cisplatin administration, TNF-α levels increase both in serum and urine (8,16).

In addition to TNF-α, interleukin (IL)-1, IL-8, and IL-18, recent studies point to the role of IL-17A and IL-33 in the pathogenesis of cisplatin-induced kidney damage (17,18). Treatment activates the inflammasome complex in the white blood cells infiltrated in the kidney and results in large amounts of IL-17A production.

In vitro studies using pharmacologic inhibitors of TNF-α (19,20) and IL-17A (18) were conducted to protect against cisplatin-induced acute kidney injury. Statins have been utilized as an anti-inflammatory agent to safeguard against kidney damage induced by cisplatin in animal models, with favorable outcomes (21-25).

Objectives

This study aimed to evaluate the protective effects of atorvastatin against cisplatin nephrotoxicity and to assess its effect on inflammatory cytokine levels, including TNF-α and IL-17A, after cisplatin administration.

Patients and Methods

Study design and participants

Patients with newly diagnosed solid tumors who were referred to the oncology department at Amir hospital affiliated with Shiraz university of medical sciences for treatment with cisplatin (50–75 mg/m^2) as a single therapeutic agent or in combination with other chemotherapy agents were included in this study. This is a randomized, double-blinded, clinical trial study with parallel design. Participants were assigned to either intervention or control group (1:1 allocation ratio). Eligible patients were recruited from May 2020 to August 2020.

Inclusion and exclusion criteria

Patients with solid tumors treated with cisplatin, aged between 18 and 60 years old, had a glomerular filtration rate (GFR) greater than 60 ml/min and serum creatinine less than 1.5 mg/dL, were included in this study. Patients receiving cisplatin in a lower dose or in divided doses, failure to take medication according to the protocol or Simultaneous use of anti-inflammatory drugs were excluded from the study.

Intervention

Cisplatin was administered intravenously into in a volume of 500 cc of normal saline over an hour. To prevent kidney damage, mannitol (25 g) was administered before cisplatin in both groups. The patients were hydrated with 1000 cc of normal saline following cisplatin administration. All patients received the same antiemetic medications, consisting of 8 mg of dexamethasone, 3 mg of granisetron (5HT3 receptor antagonists), and 125 mg of aprepitant on the first day of study, followed by aprepitant 80 mg for the subsequent two days. Participants were randomly received atorvastatin 40 mg or placebo one hour before cisplatin administration and continued to take it daily for seven days. Placebo was not distinguishable from atorvastatin in appearance and packaging.

Data collection and outcomes

The first day of study, before cisplatin administration, 8th and 20th day of study, blood samples were taken from all subjects. The samples were collected in tubes containing ethylenediaminetetraacetic acid (EDTA), followed by centrifugation at 189 g for 15 minutes at 4 °C. Finally, the serum was frozen at 70 °C. The measurements of blood urea nitrogen (BUN), serum creatinine (Cr), tumor necrosis factor TNF-α, and IL-17A were performed.
The sandwich enzyme-linked immunosorbent assay (ELISA) method was employed to measure serum levels of IL-17A and tumor necrosis factor TNF-α, using ELISA kits that are specifically designed for these cytokines manufactured by Bioscience, Campus Vienna Bio centric, Vienna, Austria. The as per the manufacturer's instructions, the concentrations of IL-17A and TNF-α were reported as pg/mL.

The BUN and serum creatinine titers were measured using the Calorimeter and Gaffe method, respectively. According to the manufacturer's instructions, the BUN and serum creatinine were reported as mg/dL, (Faraman Tehzih Pharmed, Tehran, Iran) by the Deroy auto-analyzer. The GFR was calculated using the Cockcroft formula (140 – age) × body weight/plasma creatinine × 72 (× 0.85 if female) (26).

Statistical analysis

The statistical analysis was conducted utilizing SPSS software version 24 (SPSS Inc., Chicago, IL, USA). The demographic variables between groups were compared using chi-square, Fisher's exact, and Mann-Whitney U tests. Correspondingly, the Signed Ranks test was conducted to compare variables in two groups. We used the generalized estimating equation model to compare the levels of serum creatinine, BUN, GFR, TNF-α and IL-17A in two groups of patients at different times of the treatment schedule. The generalized estimating equations model was adjusted to account for age and gender as confounders and indicator variables were utilized for each time and group interaction. We also used generalized linear models to compare variables in three time within groups. The results were analyzed by a post-hoc multiple

comparison test. A significance of a *P* value of 0.05 was considered statistically significant.

Results

After screening 48 patients, forty patients were assigned to either an intervention or a control group (1:1 allocation ratio) after screening. On the 21st day of the study, nine patients in the atorvastatin group and seven patients in the placebo group failed to complete the study. Twenty-four patients, including 11 patients (8 males and 3 female) in cisplatin plus atorvastatin (group A) and 13 patients (six males and seven females) in cisplatin plus placebo (group B) completed the study (Figure 1).

The average age of the patients was 54.5 ± 11.8 years. There was no discernible disparity observed between the two groups in terms of age, gender, drug usage in conjunction with cisplatin, or the type of disease. The demographic information for the subjects is summarized in Table 1.

The results of laboratory findings revealed, no significant difference in the trend of BUN, serum creatinine, and GFR on the 8th ($P=0.124$, $P=0.863$, $P=0.719$) and 21st days ($P=0.752$, $P=0.093$, $P=0.790$) between groups A and B, respectively.

On the eighth day of study, a decrease in GFR was observed in both groups. There was a greater slope than baseline in the placebo group, although it was not significant. Additionally, the level of serum creatinine on day 21, was higher in group B than group A, which was not statistically significant ($P=0.093$; Table 2).

Table 1. Demographic of participants in both groups

Variable	Atorvastatin	Placebo	*P* value*
Age (Mean ± SD)	55 ±11	54 ± 13	0.749
Drug-dose (mg/m²), No. (%)			
Cisplatin	71.7 ± 7.4	70.9 ± 6.8	0.600
Gender, No. (%)			
Male	8 (72.7)	6 (46.2)	0.240
Female	3 (27.3)	7 (53.8)	
Diagnosis, No. (%)			
Bladder cancer	3 (27.3)	6 (46.2)	0.402
Lung cancer	7 (63.6)	6 (46.2)	
Pancreatic cancer	1 (9.1)	0 (0)	
Unknown origin	0 (0)	1 (7.7)	

* *P* value was calculated by chi-square test.

The IL-17A and TNF-α serum levels increased on the 8th day of study, but the difference in TNF-α, and IL-17A serum levels in group A and group B on the 8th day ($P=0.731$, $P=0.546$) and 21st days of treatment ($P=0.296$, $P=0.743$) was not statistically significant, respectively.

In the intra-group comparison in Table 3, only the changes in the urea level in the placebo group and the IL-17A level in the atorvastatin group were significant, however other parameters did not have significant changes.

Regarding the average changes in the variables, patients who received atorvastatin, the level of TNF-α on day 8 decreased from 270 pg/mL to 227 pg/mL on day 21, which

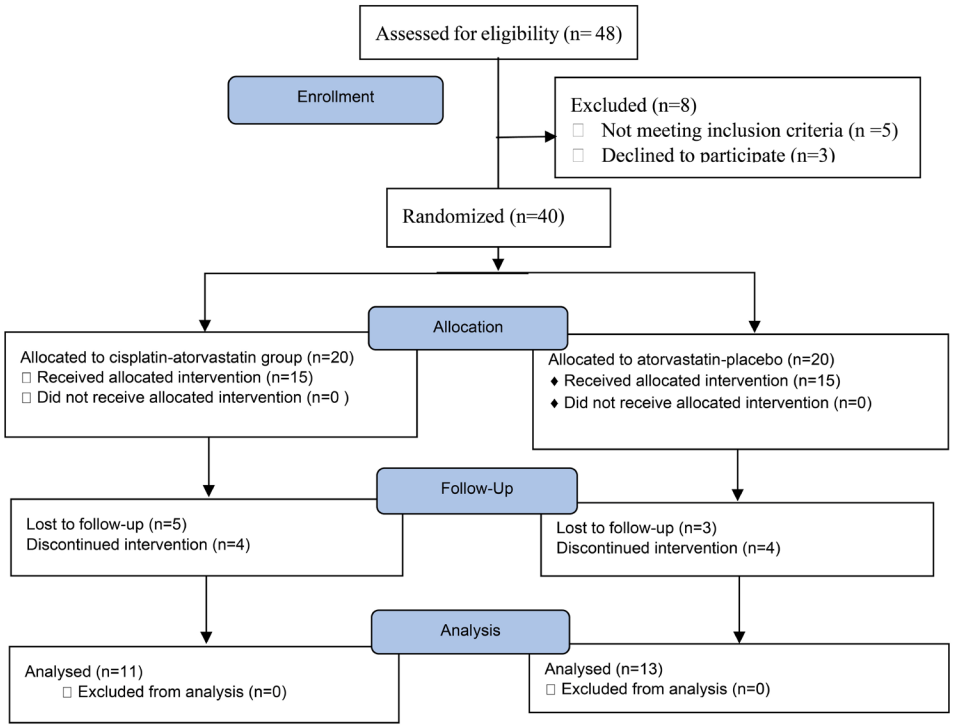

Figure 1. Consort flowchart diagram of participants.

Table 2. Comparison of BUN, serum creatinine, GFR, TNF-α, IL-17A between two groups at Days 1, 8 and 21

		Groups		*P* value*
		Atorvastatin (A)	Placebo (B)	
		Mean ± SD	Mean ± SD	
Day 1	BUN (mg/dL)	18.09 ± 6.91	17.69 ± 7.88	0.725
	Cr (mg/dL)	1.01 ± 0.18	0.99 ± 0.22	0.844
	GFR (mL/min)	70.73 ± 17.85	71.65 ± 30.81	0.954
	TNF-α (pg/mL)	235.99 ± 163.68	338.67 ± 246.94	0.223
	IL-17A (pg/mL)	345.00 ± 193.67	367.19 ± 169.80	0.913
Day 8	BUN (mg/dL)	18.64 ± 9.35	21.54 ± 10.19	0.124
	Cr (mg/dL)	1.10 ± .27	1.15 ± .35	0.863
	GFR (mL/min)	68.54 ± 31.18	65.18 ± 30.67	0.719
	TNF-α (pg/mL)	270.55 ± 158.11	307.12 ± 229.68	0.731
	IL-17A (pg/mL)	358.51 ± 194.95	420.31 ± 213.34	0.546
Day 21	BUN (mg/dL)	15.56 ± 3.24	15.22 ± 3.73	0.752
	Cr (mg/dL)	1.07 ± 0.19	1.26 ± 0.61	0.093
	GFR (mL/min)	67.90 ± 19.00	72.37 ± 29.16	0.790
	TNF-α (pg/mL)	227.19 ± 124.97	316.82 ± 208.86	0.296
	IL-17A (pg/mL)	373.07 ± 204.88	412.34 ± 217.06	0.743

BUN: Blood urea nitrogen; Cr: Serum creatinine; GFR: Glomerular filtration rate; TNF-α: Tumor necrosis factor alpha; IL-17A: interleukin-17A; SD: Standard deviation.

* *P* value was calculated by generalized linear models (generalized estimating equation).

Table 3. Comparison of BUN, serum creatinine, GFR, TNF-α, IL-17A intra-group separately in three days 1, 8 and 21

Parameter	Group	Day 1	Day 8	Day 21	F	*P* value*
		Mean ± SD	Mean ± SD	Mean ± SD		
BUN (mg/dL)	Atorvastatin (A)	18.09±6.91	18.64±9.35	15.56±3.24	0.61	0.556
	Placebo (B)	17.69±7.88	21.54±10.19	15.22±3.73	4.57	0.0277
Serum Cr (mg/dL)	Atorvastatin (A)	1.01±.018	1.10±0.27	1.07±0.19	1.27	0.298
	Placebo (B)	0.99±0.22	1.15±.35	1.26 ± 0.61	0.98	0.357
GFR (mL/min)	Atorvastatin (A)	70.73±17.85	68.54±31.18	67.90±19.00	0.11	0.769
	Placebo (B)	71.65±30.81	65.18±30.67	72.37±29.16	3.21	0.091
TNF-α (pg/mL)	Atorvastatin (A)	235.99±163.68	270.55±158.11	227.19±124.97	2.44	0.112
	Placebo (B)	338.67±246.94	307.12±229.68	316.82±208.86	1.03	0.351
IL-17A (pg/mL)	Atorvastatin (A)	345.00±193.67	358.51±194.95	373.07±204.88	4.38	0.026
	Placebo (B)	367.19±169.80	420.31±213.34	412.34±217.06	1.7	0.215

BUN: Blood urea nitrogen; Cr: Serum creatinine; GFR: Glomerular filtration rate; TNF-α: Tumor necrosis factor alpha; IL-17A: interleukin-17A; SD: Standard deviation.

* *P* value was calculated by generalized linear models.

was statistically significant. Changes in the level of IL-17A on day 21 compared to day 1 were statistically significant, although the level of IL-17A increased throughout the 21 days (Table 4).

Average changes in BUN, serum creatinine and GFR between days 1 to 8 was also statistically significant in placebo group (Table 4).

Average changes caused by the intervention in the BUN, serum creatinine, GFR, TNF-α and IL-17A, between days 1 to 8, 8 to 21 and 1 to 21within and between groups were reported in Tables 5 and 6.

Discussion

Cisplatin nephrotoxicity begins with a decrease in GFR and eventually irreversible renal failure after consecutive doses of the drug, leading to the discontinuation of the drug (26,27).

A 20% to 40% reduction in GFR relative to baseline occurs 10 days after cisplatin administration, followed by hypomagnesemia and hypokalemia, and an increase in serum creatinine level (26,27). The recovery of cisplatin nephrotoxicity is usually two to four weeks later (28,29). Repeated episodes of acute kidney injury may result in

Table 4. Comparison of the average change in the BUN, serum creatinine, GFR, TNF-α, IL-17A after intervention within groups on days 1, 8 and 21

Group	Biomarkers	Mean ± SD	*P* value*
Atorvastatin	Cr1–Cr8	-0.09 ± 0.20	0.182
	BUN1–BUN8	-0.55 ± 11.24	0.919
	GFR1–GFR8	2.19 ± 18.78	0.168
	TNF-α1–TNF-α8	-34.56 ± 74.79	0.131
	IL-17A1–IL-1-7A8	-13.50 ± 34.32	0.286
	Cr1–Cr21	-.04 ± 0.08	0.161
	BUN1–BUN21	2.00 ± 5.31	0.438
	GFR1–GFR21	2.49 ± 5.95	0.362
	TNF-α1– TNF-α21	8.80 ± 75.20	0.859
	IL-17A1–IL-1-7A21	-28.07 ± 35.12	0.003
	Cr8–Cr21	0.05 ± 0.17	0.237
	BUN8–BUN21	2.22 ± 5.30	0.235
	GFR8–GFR21	0.73 ± 17.75	0.237
	TNF-α8–TNF-α21	43.36 ± 54.03	0.033
	IL-17A8–IL-1-7A21	-14.56 ± 23.56	0.075
Placebo	Cr1–Cr8	-0.16 ± 0.25	0.028
	BUN1–BUN8	-3.85 ± 6.47	0.023
	GFR1–GFR8	7.75 ± 11.51	0.034
	TNF-α1–TNF-α8	31.54 ± 99.84	0. 600
	IL-17A1–IL-1-7A8	-53.11 ± 121.55	0.108
	Cr1–Cr21	-6.23 ± 19.53	0.185
	BUN1–BUN21	1.55 ±3.77	0.249
	GFR1–GFR21	6.27 ± 13.66	0.161
	TNF-α1–TNF-α21	21.84 ± 84.38	0.311
	IL-17A1–IL-1-7A21	-45.14 ± 138.01	0.529
	Cr8–Cr21	-6.04 ± 19.55	0.386
	BUN8–BUN21	5.88 ± 5.86	0.020
	GFR8–GFR21	-3.26 ± 6.77	0.233
	TNF-α8–TNF-α21	-9.70 ± 51.18	0.753
	IL-17A8–IL-1-7A21	7.96 ± 61.65	0.917

BUN: Blood urea nitrogen; Cr: Serum creatinine; GFR: Glomerular filtration rate; TNF-α: Tumor necrosis factor alpha; IL-17A: interleukin-17A; SD: Standard deviation.

* *P* value was calculated by nonparametric test, Wilcoxon signed-rank test.

chronic kidney disease.

The process of acute kidney injury induced by cisplatin is a highly intricate. The induction of pro-inflammatory cytokines including TNF-α, IL-1, MCP1 (monocyte chemoattractant protein 1) and IL-6, in conjunction with the infiltration of inflammatory cells, including macrophages and neutrophils, results in renal tissue damage and the death of renal tubular cells in animal models (30,31). TNF-α is a key major of the inflammatory response to cisplatin nephrotoxicity. It has been demonstrated that the decrease in production of cytokines and chemokines in a TNF-α deficient mouse or the inhibition of TNF-α production with pharmacologic agents results in amelioration of renal failure during cisplatin administration (6,32,33).

Preventive measures to mitigate renal damage are of utmost importance for the continued use of cisplatin treatment with a suitable dose and schedule.

Statins have been demonstrated to have a favorable effect on the reduction of inflammation in individuals who are suffered with various diseases, such as coronary artery disease, chronic renal disease, and diabetes mellitus (34).

On the contrary, it has been demonstrated that the administration of statins in animals can mitigate the adverse effects of cisplatin-induced kidney damage by reducing the levels of TNF-α in both serum and tissue. In mice that received cisplatin intraperitoneally, the use of simvastatin and rosuvastatin resulted in a significant decrease in urea and serum creatinine levels compared to the control group. Furthermore, these two drugs significantly reduced the levels of myeloperoxidase, TNF-α, NF-κB (nuclear factor kappa B) and IL-1B in kidney tissue. In this study, it was observed that the rosuvastatin had a superior effect compared to simvastatin (23).

Table 5. Calculation of the average changes caused by the intervention in the BUN, serum creatinine, GFR, TNF-α and IL-17A intra-groups between days 1-8, 8-21, 1-21

	Mean ± SD	Day	MD (95% CI)	*P* value* (1-8)	*P* value* (1-21)	*P* value* (8-21)
Atorvastatin group						
BUN (1st)	18.09±6.91	Day 1-8	- 0.5 (-6.2–5.1)	0.850	–	–
BUN (8th)	18.64±9.35	Day 1-21	2.98 (-2.99–8.94)	–	0.327	–
BUN (21st)	15.56±3.24	Day 8-21	3.5 (-2.44–9.5)	–	–	0.247
Cr (1st)	1.01±.018	Day 1-8	-0.09 (-6.02–5.8)	0.977	–	–
Cr (8th)	1.10±0.27	Day 1-21	-0.2 (-6.5–6.06)	–	0.950	–
Cr (21st)	1.07±0.19	Day 8-21	-0.11 (-6.4–6.1)	–	–	0.972
GFR (1st)	70.73±17.85	Day 1-8	2.2 (-16.4–20.8)	0.817	–	–
GFR (8th)	68.54±31.18	Day 1-21	1.3 (-18.3–20.9)	–	0.897	–
GFR (21st)	67.90±19.00	Day 8-21	-0.9 (-20.5–18.7)	–	–	0.929
TNF-α (1st)	235.99±163.68	Day 1-8	-34.6 (-186.9–117.8)	0.657	–	–
TNF-α (8th)	270.55±158.11	Day 1-21	8.8 (-143.6–161.2)	–	0.910	–
TNF-α (21st)	227.19±124.97	Day 8-21	43.4 (-109.01–195.7)	–	–	0.577
IL-17A (1st)	345.00±193.67	Day 1-8	-13.5 (-170.1–143.03)	0.866	–	–
IL-17A (8th)	420.31±213.34	Day 1-21	-28.1 (-184.6–-128.5)	–	0.725	–
IL-17A (21st)	412.34±217.06	Day 8-21	-14.6 (-171.1–141.9)	–	–	0.855
Placebo group						
BUN (1st)	17.69±7.88	Day 1-8	-3.8 (-9.1–1.4)	0.147	–	–
BUN (8th)	21.54±10.19	Day 1-21	2.9 (-2.76–8.75)	–	0.309	–
BUN (21st)	15.22±3.73	Day 8-21	6.8 (1.1–12.6)	–	–	**0.020**
Serum Cr (1st)	0.99±0.22	Day 1-8	-0.16 (-5.6–5.3)	0.954	–	–
Serum Cr (8th)	1.10±0.27	Day 1-21	-6.3 (-12.2–-0.5)	–	**0.034**	–
Serum Cr (21st)	7.26±19.55	Day 8-21	-6.2 (-12.03–-0.32)	–	–	**0.039**
GFR (1st)	71.65±30.81	Day 1-8	6.1 (-11.4–23.6)	0.493	–	–
GFR (8th)	65.18±30.67	Day 1-21	-0.98 (-19.9–17.9)	–	0.919	–
GFR (21st)	72.37±29.16	Day 8-21	-7.1 (-26.3–12.2)	–	–	0.470
TNF-α (1st)	338.67±246.94	Day 1-8	31.5 (-108.6–171.7)	0.659	–	–
TNF-α (8th)	307.12±229.68	Day 1-21	21.8 (-118.3–162.02)	–	0.760	–
TNF-α (21st)	316.82±208.86	Day 8-21	-9.7 (-149.9–130.5)	–	–	0.892
IL-17A (1st)	367.19±169.80	Day 1-8	-35.1 (-197.1–90.9)	0.470	–	–
IL-17A (8th)	420.31±213.34	Day 1-21	-45.1 (-189.1–98.9)	–	0.539	–
IL-17A (21st)	412.34±217.06	Day 8-21	7.96 (136.03–151.97)	–	–	0.914

BUN: Blood urea nitrogen; Cr: Serum creatinine; GFR: Glomerular filtration rate; TNF-α: Tumor necrosis factor alpha; IL-17A: interleukin-17A; SD: Standard deviation.

* *P* value was calculated by generalized linear models (generalized estimating equation).

A study conducted by Abady et al demonstrated that administration of atorvastatin four days prior to intraperitoneal cisplatin injection in rabbits resulted in a significant reduction in serum creatinine and TNF-α levels. Furthermore, treatment with atorvastatin moderately ameliorated the histopathological damage to renal tissue caused by cisplatin (35).

According to studies conducted by Boorla et al and Iseri et al, statins are a potent medication for preventing cisplatin-induced nephrotoxicity (25,36).

Recent studies have demonstrated that, in addition to TNF-α, IL-1, IL-8, and IL-18, other cytokines such as IL-17A and IL-33 also play an important role in the pathogenesis of cisplatin-induced acute kidney injury (18,37). The administration of cisplatin results in the activation of the inflammasome complex present in the white blood cells infiltrated in the kidney, resulting in the production of significant amounts of IL-17A. The

Table 6. Comparison of the average changes caused by the intervention in the BUN, serum creatinine, GFR, TNF-α and IL-17A between two groups in three times (1-8-21)

	Group		*P* value*
	Atorvastatin	Placebo	
	Mean ± SD	Mean ± SD	
Group			
Cr1-Cr8	-0.09 ± 0.20	-0.16 ± 0.25	0.780
BUN1-BUN8	-0.55 ± 11.24	-3.85 ± 6.47	0.161
GFR1-GFR8	2.19 ± 18.78	7.75 ± 11.51	0.931
TNF-α1- TNF-α8	-34.56 ± 74.79	31.54 ± 99.84	0.035
IL-17A1-IL-1-7A8	-13.50 ± 34.32	-53.11 ± 121.55	0.608
Group			
Cr1-Cr21	-0.04 ± 0.08	-6.23 ± 19.53	0.447
BUN1-BUN21	2.00 ± 5.31	1.55 ±3.77	0.796
GFR1-GFR21	2.49 ± 5.95	6.27 ± 13.66	0.546
TNF-α1-TNF-α21	8.80 ± 75.20	21.84 ± 84.38	0.776
IL-17A1-IL-1-7A21	-28.07 ± 35.12	-45.14 ± 138.01	0.424
Group			
Cr8-Cr21	0.05 ± 0.17	-6.04 ± 19.55	0.820
BUN8-BUN21	2.22 ± 5.30	5.88 ± 5.86	0.277
GFR8-GFR21	0.73 ± 17.75	-3.26 ± 6.77	0.651
TNF-α8- TNF-α21	43.36 ± 54.03	-9.70 ± 51.18	0.186
IL-17A8-IL-1-7A21	-14.56 ± 23.56	7.96 ± 61.65	0.331

BUN: Blood urea nitrogen; Cr: Serum creatinine; GFR: Glomerular filtration rate; TNF-α: Tumor necrosis factor alpha; IL-17A: interleukin-17A; SD: Standard deviation.
* *P* value was calculated by nonparametric test, Wilcoxon signed-rank test.

observation that the administration of anti-IL-17A antibody can mitigate the adverse effects of cisplatin-induced nephrotoxicity corroborates the significant pathogenic role of IL-17A in cisplatin-induced acute kidney injury (37).

Our study is the first to examine the effect of atorvastatin on cisplatin nephrotoxicity in humans, and as all previous studies have been conducted in rats and rabbits.

In our study, there was no statistically significant difference between two groups at the levels of serum creatinine, urea, TNF-α and IL17A between the 8th and 21st days of study.

In an intragroup analysis, there was a significant increase at the level of serum creatinine in the placebo group, but not in the Atorvastatin group. The decrease in the GFR was more pronounced on the eighth day of the study in the placebo group compared to the Atorvastatin group. It seems that atorvastatin exhibits a protective effect on the renal system.

The observation that in the placebo group, the elevation in serum creatinine level and decrease in GFR, despite no correlation with cytokine levels, occurred subsequent to cisplatin administration may be attributed to the limited number of patients.

It is recommended to conduct a study with a substantial number of patients and a prolonged follow-up period.

Conclusion

Atorvastatin has the ability to prevent nephrotoxicity, however, it does not have any effect on inflammatory cytokines.

Limitations of the study

The limited number of patients and the short duration of follow-up were limitations of our study.

Authors' contribution

Conceptualization: Seyedeh Azra Shamsdin and Nasrin Namdari.
Data curation: Nasrin Namdari and Ali Rajaei.
Formal analysis: Seyedeh Azra Shamsdin and Nasrin Namdari.
Investigation: Ali Rajaei.
Methodology: Nasrin Namdari and Ali Rajaei.
Project administration: Ali Rajaei.
Resources: Seyedeh Azra Shamsdin and Nasrin Namdari.

Software: Seyedeh Azra Shamsdin and Nasrin Namdari.
Supervision: Nasrin Namdari.
Validation: Seyedeh Azra Shamsdin.
Visualization: Nasrin Namdari.
Writing–original draft: Seyedeh Azra Shamsdin and Nasrin Namdari.
Writing–review & editing: Nasrin Namdari, Seyedeh Azra Shamsdin.

Conflicts of interest

The authors declare that they do not possess any competing interests.

Ethical issues

The research was conducted according to the principles of the Declaration of Helsinki. The institutional ethical committee at Shiraz University of Medical Sciences accepted all study protocols (Ethical code #IR.SUMS.MED.REC.1398.024). Besides, written informed consent was taken from all participants before any intervention. The trial protocol was approved by the Iranian registry of clinical trials (identifier: IRCT20140605017982N2; https://en.irct.ir/trial/47349). The authors have meticulously observed ethical concerns, including but not limited to plagiarism, data fabrication, and double publication.

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