RESEARCH ARTICLE

Dextrose Hydration May Promote Cisplatin-induced Nephrotoxicity in Rats: Gender-related Difference

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Abstract

BACKGROUND: Cisplatin (CP) as an anticancer drug may affect the plasma glucose level while diabetic subjects are protected against CP-induced nephrotoxicity. In the current study, the role of dextrose hydration during CP therapy on CP-induced nephrotoxicity was evaluated.

METHODS: Sixty-nine male and female rats were divided into 12 groups. The rats were hydrated with 15 mL/kg vehicle or different doses of 2%, 10% and 20% dextrose before and after 7.5 mg/kg CP administration. One week later, the biochemical and kidney function markers, and histology finding were determined.

RESULTS: All the animals co-treated with CP and 20% dextrose, were dead during one week of the experiment. Administration of CP alone increased kidney tissue damage score (KTDS) and kidney weight (KW). It also elevated the blood urea nitrogen (BUN) and BUN-creatineine ratio (BUN/Cr) levels in the serum. In addition, CP decreased body weight and creatinine (Cr) clearance (ClCr) significantly in both male and female rats ($p<0.05$). However, 2% and 10% dextrose did not alter the mentioned parameters in male, but 10% dextrose supplement increased the serum levels of BUN, Cr and BUN/Cr ratio, KW and KTDS significantly in female rats ($p<0.05$).

CONCLUSION: Our data suggest that not only do not support the nephro-protective role of dextrose hydration during CP therapy, the dextrose hydration can act as risk factor to promote CP-induced nephrotoxicity in female rats. Prohibition of high carbohydrate (glucose) diet during CP therapy is recommended.

KEYWORDS: cisplatin, nephrotoxicity, dextrose, rat, gender

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Introduction

Cisplatin (CP) has been used widely in clinic for solid tumor chemotherapy; however one of the side effects of CP is nephrotoxicity which limits its clinical use. The CP-induced nephrotoxicity was reported to be gender related (1-4), and antioxidants supplements may attenuate the side effect of nephrotoxicity (1,5-9). The experimental findings also indicated that the sex hormone, estrogen, affects the CP-induced nephrotoxicity.(10-13) In addition, this female sex hormone may promote CP-induced nephrotoxicity (11) or limit the protective effect of antioxidant against CP-induced kidney injury (13).

CP may decrease glucose uptake in ovarian cancer cell, and it disappears the membrane localization of glucose transporter 1.(14) In addition, CP itself may induce hyperglycemia and glucose intolerance (15), and this

impairment maybe related to insulin secretion deficiency. (16) Previously, it was reported that in diabetic animals were protected against CP-induced nephrotoxicity.(17-20) Diabetes disturbs the active transport of proximal tubule and reduce CP accumulation in the tubule (21), therefore, it protects the kidney against CP-induced nephrotoxicity. However, among the factors affecting CP-induced nephrotoxicity, the role of glucose is not well clear.

Usually, based on the treatment guideline, the candidate patients for CP therapy must be hydrated during CP administration.(22) If hyperglycemia is the main cause of kidney protection against CP-induced nephrotoxicity in diabetic subjects, it is expected that the patients who hydrated with high glucose solution (instead saline) would be protected against CP-induced nephrotoxicity. On the other hand, practically it is observed that many of the patients who are candidate for CP therapy have an appetite to eat cookie or high sweet diets during the CP administration time in the hospital.

Collectively, there are 2 facts. First, CP administration is accompanied with side effect of nephrotoxicity gender dependently.(1-4) Secondly, the diabetic subjects are protected against CP-induced nephrotoxicity.(17-20) One explanation for this difference is related to the dose of glucose concentration which is different in normal and diabetic conditions. Therefore, one question was raised, is high dose of glucose uptake during CP therapy could protect the kidney against CP-induced nephrotoxicity or not, and what is the role of gender? In order to answer these questions, male and female rats were subjected to hydrate with different doses of dextrose solution during CP therapy, and they were compared with control group.

Methods

The protocol of this research was considered and approved by the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.REC.1397.2.055).

Drugs

The CP and dextrose were purchased from Malan (Athens, Greece) and Shahid Ghazi Pharmaceutical Co (Tabriz, Iran).

Experimental Groups

This research was conducted on 69 male and female Wistar rats in 12 groups (6 groups of male and 6 groups of female rats). Group 1 and 7 (vehicle groups) were consisted of 5 male and 6 female rats. Eleven rats were subjected to 3 treatments. The first treatment of vehicle (saline, 15 mL/kg, intraperitoneally) was applied at the beginning of experiment. The second treatment of vehicle (0.5-1 mL/rat) was applied 60 min post the first treatment. Finally, the third treatment of vehicle (saline, 15 mL/kg, intraperitoneally) was applied 60 min post the second treatment.

Group 2 and 8 were the dextrose 10% groups, which were consisted of 5 male and 6 female rats. They received the same regimen as groups 1 and 7, except they were given dextrose 10% (15 mL/kg, intraperitoneally) instead of vehicle (saline) for the first and third treatments.

Group 3 and 9, or known as CP groups, were consisted of 5 male and 6 female rats, which received the same regimen as group 1 and 7, except they were given CP (7.5 mg/kg, intraperitoneally), instead of vehicle (saline) for the second treatment.

Group 4 and 10, the CP + dextrose 2% groups, were consisted of 6 male and 6 female. These 12 rats were also subjected to 3 treatments. The first treatment of dextrose 2% (15 mL/kg, intraperitoneally) was applied at the beginning of experiment. The second treatment of CP (7.5 mg/kg, intraperitoneally) was applied 60 min post the first treatment, and the third treatment of dextrose 2% (15 mL/kg, intraperitoneally) was applied 60 min post the second treatment.

Group 5 and 11, the CP + dextrose 10% groups, were consisted of 6 male and 6 female rats, which were treated just like groups 4 and 10, except they received 15 mL/kg of dextrose 10% instead of dextrose 2% for the first and third treatments.

Group 6 and 12, CP + dextrose 20% groups, were consisted of 5 male and 6 female rats, which were treated as groups 4 and 10, except they received 15 mL/kg of dextrose 20% instead dextrose 2% for the first and third treatments.

Survival Time Determination

The animals were kept in standard cages with free access to water and food. All the animals were observed continually (3-4 times a day) and weighted in the first and 8th days of experiment. The mortality rate for each animal group was recorded daily.

Urine, Blood and Kidney Tissue Samples Collections

The remained survived animals until the 8th day were subjected to place in metabolic cages for 5 hours before sacrifice for urine collection. The total amount of urine collection in each animal was measured precisely and reported as microliter per minute per gram kidney tissue. Then, blood samples were obtained and the animals

sacrificed humanly. The kidneys were removed rapidly and weighted. The tissues were fixed in formalin 10% to perform histological investigation using hematoxylin and eosin (H&E) staining. The kidney tissue damage score (KTDS) was recorded by two pathologist who were blinded to study protocol. The score was assigned from 1 to 4 based on intensity of tissue damage while zero was considered as normal.

Biochemical Parameters Measurements

The levels of blood urea nitrogen (BUN) and creatinine (Cr), were determined using quantitative diagnostic kits (Pars Azmoon, Tehran, Iran). The malondialdehyde (MDA) levels in the serum and kidney tissue were measured by the manual method. The serum and kidney tissue levels of nitrite (stable nitric oxide (NO) metabolite) were measured using Griess method. The levels of sodium (Na) in serum and urine were determined using flame photometer assay.

Kidney Function Parameters Measurements

The Cr clearance (ClCr) was determined using clearance formula as; ClCr = UF * UCr/ PCr where UF, UCr and PCr were assigned for urine flow rate, urine Cr concentration and serum level of Cr. The Na filtration rates (FNa) and Na excretion rate (ENa) were calculated by [ClCr x serum concentration of Na] and [UF x urine concentration of Na] respectively.

Statistical Analysis

Data were reported as mean±SEM. The ANOVA and Dunnet test as post hoc were applied for comparison between the groups. The survival time and KTDS between the groups were compared by non-parametric tests of Kruskal-Wallis and Mann-Whitney U. The statistical *p*-value was significant when it was less than 0.05.

Results

Animal's Survival Time

The data for animal's survival time are tabulated in Table 1. The entire male (survival time = 4.8±0.4 days) and female (survival time = 4.0±0.0 days) animals treated with CP + extrose 20% expired during the experiment and no animals were survived for the last day of experiment (sacrifice day). Therefore no data were reported here for these groups. No animals were died in the control groups of male (groups 1-3) and female (groups 7-9) rats. However, 3 male and 2 female animals that treated with CP + dextrose 2%-10% were expired during the experiment before sacrifice day (Table 1).

Body and Kidney Weights

The body weight percentage change (ΔW%) and normalized kidney weight (KW) in vehicle, dextrose 10% or CP alone (male's group 1-3 and female's group 7-9) treated groups were compared to determine the effect CP or dextrose alone administration (Table 2A). The results indicated that CP increased the absolute ΔW and KW significantly ($p<0.05$) in both genders.

The animals treated with CP alone also were compared with the animals co-treated with CP and dextrose (Figure 1A). Co-administration of CP and dextrose did not attenuate the KW when compared with CP alone treated group (Figure 1A). Instead, in the female rats, co-administration of CP and dextrose 10% not only attenuate the KW but also increased the KW (1.36±0.16 g) significantly when compared with CP alone (0.94±0.04 g) treated group ($p<0.05$) (Figure 1A).

Biochemical Parameters

The serum levels of BUN, Cr and BUN/Cr ratio in vehicle, dextrose 10% or CP alone treated groups (male's group 1-3 and female's group 7-9) were compared to determine the effect CP or dextrose alone administration (Table 2B). The results indicated that CP increased the above parameters (except the serum level of Cr in female) significantly ($p<0.05$).

The animals treated with CP alone also were compared with the animals co-treated with CP and dextrose (Figure 1B). Co-treatment of CP and dextrose did not attenuate the serum level of BUN, Cr and BUN/Cr ratio in male. However, in female rats, the co-administration of CP and dextrose 10% increased the serum level of BUN (92.4±35.9 mg/dL *vs*. 28.4±1.8 mg/dL, $p<0.05$), Cr (1.6±0.4 mg/dL *vs.* 0.75±0.05 mg/dL, $p<0.05$) and BUN/Cr ratio (52.7±7.3 *vs.* 38.2±2.0, $p<0.05$) significantly) when compared with CP alone treated group.

The serum and kidney tissue levels of nitrite and MDA in vehicle, dextrose 10% or CP alone treated groups (male's group 1-3 and female's group 7-9) also were compared to determine the effect CP or dextrose alone administration (Table 2C). The results indicated that CP altered the serum and kidney levels of nitrite and the serum level of MDA significantly ($p<0.05$) in male groups.

The animals treated with CP alone also were compared with the animals co-treated with CP and dextrose (Figure 1C). The serum and kidney tissue levels of MDA in male rats were not different statistically between CP alone treated

Table 1. The mean values of survival time for each group of male and female rats during the experiment.

Treatment	Group	n	Number of Death Animals (Male)							Survived	Survival Time (day)	Group	n	Number of Death Animals (Female)							Survived	Survival Time (day)	*p* -value (between genders)
			Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7					Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7			
Vehicle	**1**	5	-	-	-	-	-	-	-	5	8.0±0.0	**7**	6	-	-	-	-	-	-	-	6	8.0±0.0	1
DS 10%	**2**	5	-	-	-	-	-	-	-	5	8.0±0.0	**8**	6	-	-	-	-	-	-	-	6	8.0±0.0	1
CP	**3**	5	-	-	-	-	-	-	-	5	8.0±0.0	**9**	6	-	-	-	-	-	-	-	6	8.0±0.0	1
CP+DS 2%	**4**	5	-	-	-	-	-	-	2	3	7.6±0.5	**10**	6	-	-	-	-	-	-	-	6	8.0±0.0	0.14
CP+DS 10%	**5**	6	-	-	-	-	-	-	1	5	7.8±0.2	**11**	6	-	-	-	-	-	1	1	4	7.5±0.3	0.6
CP+DS 20%	**6**	6	-	-	-	3	1	-	2	0	$4.8\pm0.4^{a,b,c,d,e}$	**12**	6	-	-	-	6	-	-	-	0	$4\pm0.0^{a,b,c,d,e}$	0.18
						$P_{\text{Kruskal-Wallis H}}$					<0.0001						$P_{\text{Kruskal-Wallis H}}$					0.0001	

The small alphabetic letters indicate significant difference from vehicle (a), dextrose 10% (b), cisplatin (c), cisplatin + dextrose 2% (d), and cisplatin + dextrose 10% (e) ($p<0.05$). The each two groups were compared using Mann-Whitney U analysis. CP: cisplatin; DS: dextrose.

Table 2. The effects of dextrose 10% and CP administration against vehicle on body and kidney weight (A), serum levels of BUN, Cr, BUN/Cr ratio (B), and serum and kidney levels of nitrite and MDA (C).

A

Parameter	Gender	Vehicle	Dextrose 10%	CP	P_{ANOVA}
ΔW (%)	Male	-1.0±1.0	3.7±1.0*	-19.0±1.2*	<0.0001
	Female	1.9±0.9	-1.8±1.2	-9.0±3.4*	0.008
KW (g)/100g BW	Male	0.68±0.02	0.67±0.02	1.06±0.04*	<0.0001
	Female	0.76±0.02	0.83±0.02	0.94±0.04*	0.002

B

Parameter	Gender	Vehicle	Dextrose 10%	CP	P_{ANOVA}
BUN (g/dL)	Male	17.94±0.6	25.14±0.7	43.1±6.6*	0.002
	Female	20.48±1.14	20.71±0.73	28.4±1.8*	0.001
Cr (g/dL)	Male	0.87±0.06	0.65±0.03*	1.25±0.07*	<0.0001
	Female	0.72±0.02	0.74±0.01	0.75±0.05	0.83
BUN/Cr	Male	20.9±1.6	38.7±1.9*	33.6±4.2*	0.002
	Female	28.4±2.1	27.9±1.4	38.2±2.0*	0.002

C

Parameter	Gender	Vehicle	Dextrose 10%	CP	P_{ANOVA}
Serum Nitrite (µmol/L)	Male	9.23±1.07	11.43±0.82	17.89±2.10*	0.003
	Female	11.04±1.55	8.43±0.67	13.19±2.83	0.24
Kidney Nitrite (µmol/g)	Male	0.15±0.02	0.19±0.01	0.10±0.01*	0.024
	Female	0.18±0.03	0.18±0.01	0.16±0.02	0.85
Serum MDA (µmol/L)	Male	0.19±0.17	0.25±0.14	1.91±0.89*	0.06
	Female	2.31±0.47	1.68±0.25	3.63±1.26	0.23
Kidney MDA (nmol/g)	Male	55.34±1.71	72.96±15.04	48.88±3.66	0.19
	Female	94.10±10.98	92.63±21.15	71.10±4.24	0.44

The *p*-value was obtained by ANOVA, and the star (*) indicates significant differences ($p<0.05$) from vehicle group using Dunnet test. CP: cisplatin, ΔW; weight change, KW: kidney weight, BUN: blood urea nitrogen, Cr: creatinine.

group and co-treated of CP and dextrose groups. However, in female rats the serum and kidney tissues levels of MDA were decreased in co-treated of CP and dextrose groups when compared with CP alone treated rats (Figure 1C), but the decrease was significant for the serum level of MDA in co-treated group of CP and dextrose 2% (0.60±0.15 µmol/L *vs.* 3.6±1.3 µmol/L, $p<0.05$), and the decrease for the kidney tissue level of MDA was significant in co-treated group of CP and dextrose 10% (37.6±1.4 nmol/g tissue *vs.* 71.1±4.2 nmol/g tissue, $p<0.05$).

The serum levels of nitrite decreased (significantly), and the tissue levels of nitrite were increased (insignificantly) in co-treated of CP and dextrose male rats when compared with CP alone treated group (Figure 1C). Such observation was not seen in female rats but co-treatment of CP and dextrose 2% increased the kidney tissue level of nitrite statistically ($p<0.05$).

Kidney Function Parameters

The UF, ClCr, FNa, ENa and Na excretion fraction (%) in vehicle, dextrose 10% or CP alone treated groups (male's group 1-3 and female's group 7-9) were compared to determine the effect CP or dextrose alone administration (Table 3A). The ClCr and FNa in both genders, ENa in female and Na excretion fraction (%) in male were significantly different between CP treated rats and vehicle treated group ($p<0.05$).

The animals treated with CP alone also were compared with the animals co-treated with CP and dextrose (Figure 2). The results of renal function markers; UF, ClCr, FNa, ENa and percentage of Na excretion fraction are presented in Figure 2. They are indicated that co-administration of CP and dextrose compared to CP alone did not alter the renal function markers neither in male nor in female rats. Actually in female, all the above markers in co-treated group of CP

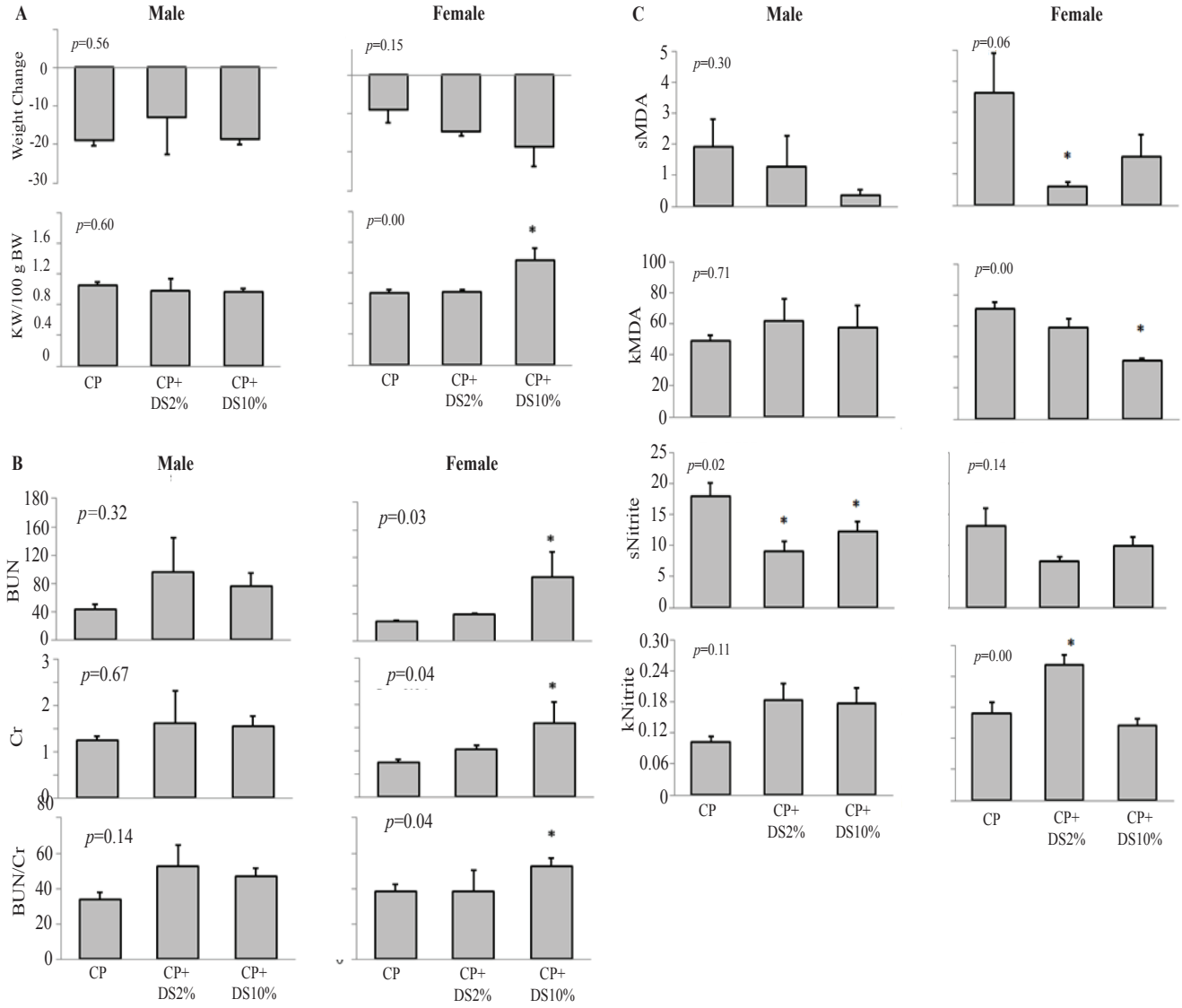

Figure 1. Characteristic difference between male and female rats of survived animals in the experimental groups. A: percentage of weight change (%) and kidney weight (KW) (g) per 100 g of body weight (BW). B: serum levels of blood urea nitrogen (BUN) (mg/dL), creatinine (Cr) (mg/dL) and BUN/Cr ratio. C: serum (µmol/L) and kidney tissue (µmol/g tissue) levels of malondealdehyde (MDA) and nitrite for survived animals in the experimental groups. The CP, CP+DS2% and CP+DS10% indicate the groups treated with cisplatin, cisplatin plus dextrose 2% and cisplatin plus dextrose 10%, respectively. The *p*-value was obtained by ANOVA. The star (*) indicates significant differences ($p<0.05$) from CP using Dunnet test.

and dextrose 10% were decreased when compared with CP alone treated group, however these change were not statistically significant (Figure 2).

Kidney Histology Findings

The KTDS in vehicle, dextrose 10% or CP alone treated groups (male's group 1-3 and female's group 7-9) were compared to determine the effect CP or dextrose alone administration (Table 3B). The results indicated that CP increased the KTDS significantly ($p<0.05$) in both genders. The animals treated with CP alone also were compared with the animals co-treated with CP and dextrose (Figure 3). The KTDS did not alter in co-treated of CP and dextrose male rats compared to CP alone treated group, however in female rats, the KTDS was increased significantly in co-treated with CP and dextrose 10% group compared to CP alone treated group (3.3±0.2 *vs.* 2.3±0.2; $p<0.05$). More tubular tissue damage was observed in female rats treated with CP and dextrose 10% compared to the CP alone treated animals.

Table 3. The effects of dextrose 10% and cisplatin (CP) administration against vehicle on urine flow (UF), creatinine clearance (ClCr), sodium (Na) filtration rate (FNa), Na excretion rate (ENa) and percentage of Na excretion fraction (%) (A), and kidney tissue damage score (KTDS) (B).

A

Parameter	Gender	Vehicle	Dextrose 10%	CP	P_{ANOVA}
UF (µL/mim/g)	Male	2.9±0.7	5.05±1.0	4.50±0.8	0.21
	Female	5.3±0.7	2.37±0.4*	4.01±1.0	0.04
ClCr (µL/mim/g)	Male	732.6±125.1	951.9±75.3	197.8±26.6*	<0.0001
	Female	1148.3±144.6	706.8±100.8*	510.1±142.0*	0.011
FNa (µmole/mim/g)	Male	120.6±22.9	157.9±9.4	33.8±4.8*	<0.0001
	Female	172.9±23.2	115.9±15.4	92.5±25.8*	0.05
ENa (µmole/mim/g)	Male	0.46±0.15	1.16±0.14*	0.59±0.15	0.014
	Female	0.99±0.12	0.35±0.08*	0.35±0.07*	<0.0001
Na Excretion Fraction (%)	Male	0.36±0.07	0.74±0.09	1.67±0.28*	0.001
	Female	0.63±0.11	0.41±0.18	1.75±1.45	0.5

B

Parameter	Gender	Vehicle	Dextrose 10%	CP	$P_{Kruskal-Wallis}$
KTDS	Male	0.8±0.2	0.6±0.2	3.2±0.4*	<0.0001
	Female	1±0.3	0.7±0.3	2.3±0.2*	<0.0001

The *p*-value in part A was obtained by ANOVA, and the star (*) indicates significant differences ($p<0.05$) from vehicle group using Dunnet test. The *p*-value in part B was obtained Kruskal–Wallis, and the star (*) indicates significant differences ($p<0.05$) from vehicle group using Mann–Whitney U test. CP: cisplatin; UF: urine flow rate; ClCr: Creatinine clearance; FNa: sodium filtration rate; ENa: sodium excretion rate; KTDS: kidney tissue damage score.

Discussion

The purpose of this study was to determine the possible protective role of dextrose hydration during CP therapy against CP induced nephrotoxicity. Our hypothesis was rejected while dextrose promoted CP-induced nephrotoxicity, and the major findings of this research revealed that dehydration with dextrose during CP therapy acts as risk factor to promote kidney toxicity.

No animals were survived when dextrose 20% was accompanied with CP, possibly due to toxic effect of high dose of dextrose. The animals weight loss was observed in the all survived animals treated with CP which was expected

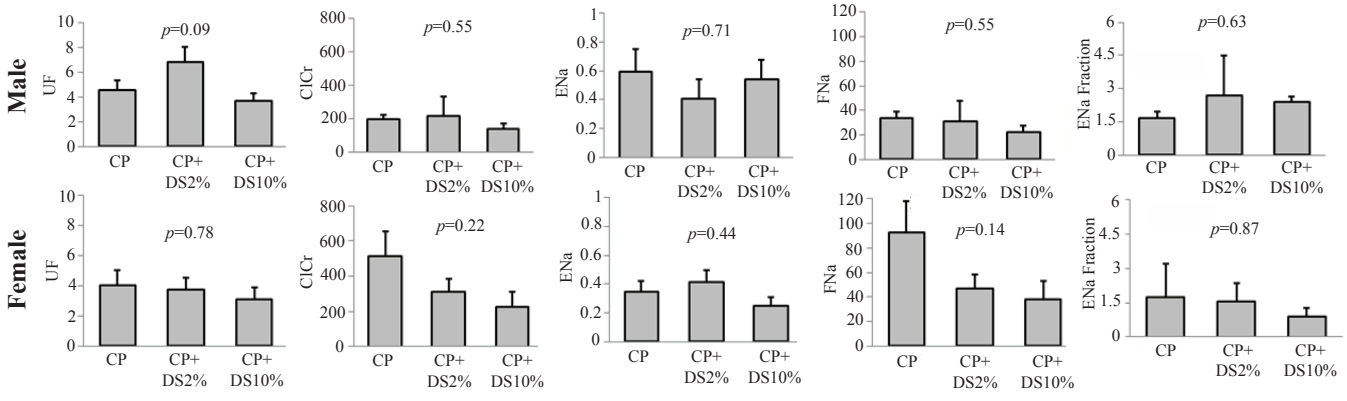

Figure 2. The urine flow (UF), creatinine clearance (ClCr), sodium (Na) filtration rate (FNa), Na excretion rate (ENa) and percentage of Na excretion fraction in cisplatin, cisplatin plus dextrose 2% and cisplatin plus dextrose 10% treated groups, respectively. The *p*-value was obtained by ANOVA. The star (*) indicates significant differences ($p<0.05$) from CP using Dunnet test. CP: cisplatin; DS: dextrose. The unit for UF=µL/mim/g tissue, ClCr=µL/mim/g tissue, ENa=µmol/mim/g tissue, FNa=µmol/mim/g tissue; FNa fraction=%.

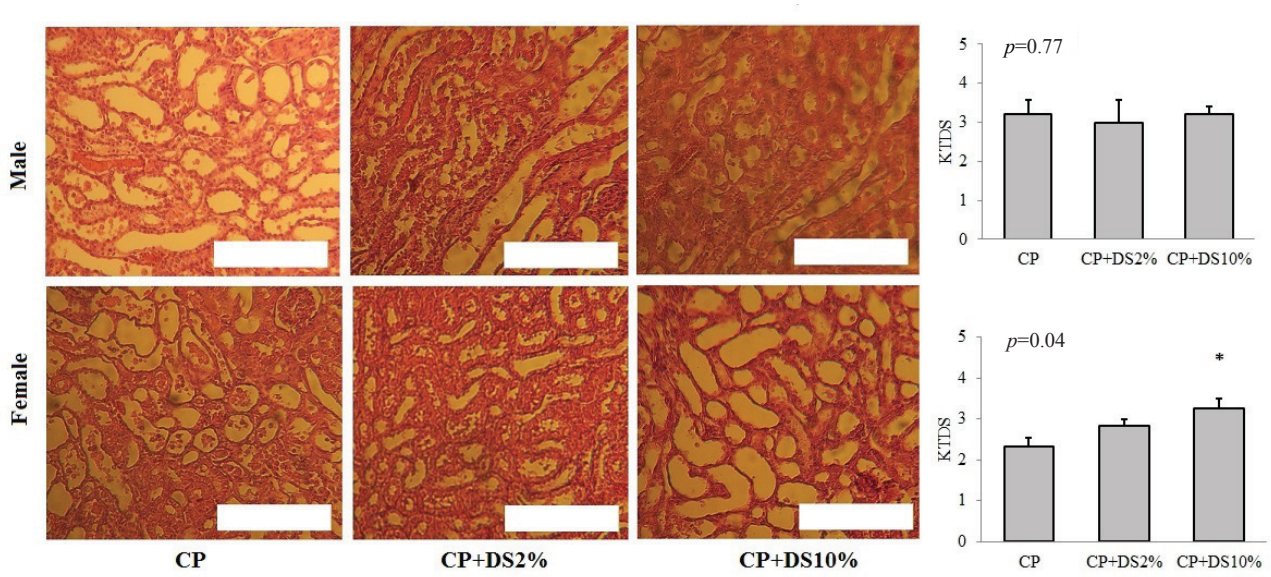

Fig 3. The kidney tissue damage score (KTDS) (right panel) for survived animal in the experimental groups. The CP, CP+DS2% and CP+DS10% indicate the groups treated with cisplatin, cisplatin plus dextrose 2% and cisplatin plus dextrose 10%, respectively. The *p*-value was obtained by Kruskal–Wallis test. The star indicates significant differences ($p<0.05$) from CP using Mann-Whitney U test.White bar: 0.25 mm x 1.0 mm.

as observed in other studies.(1-4) In addition the elevations of the serum levels of BUN and Cr and KW are associated with increase of kidney damage after CP administration (4), and our results indicated that dextrose 10% elevated these parameters in female gender. It seems these alterations are related to the decrease of ClCr (or glomerular filtration rate) in female rats treated with CP and dextrose 10% (Figure 2). These findings in female rats also are in agreement with pathology data and KTDS (Figure 3).

It has been proposed that diabetes protects the kidneys against CP administration (18-20), and the degree of protection depends on degree of hyperglycemia. Previous study reported that the diabetic state could protect that kidney against CP-induced nephrotoxicity, and the kidney toxicity would be higher if the hyperglycemia was corrected by insulin.(20) The vacuolated cells, tubular dilation and necrosis-induced by CP administration in rat. However these tissue damages were attenuated in diabetic state.(20) One mechanism is related to kidney drug accumulation, because in diabetic state, the reduction of platinum accumulation in the kidney is occured.(23) One study demonstrated that hyperglaycemia reduction by insulin treatment in diabetic rats may not protect the kidney against CP-induced nephrotoxicity.(18) Therefore, it seems that an interaction between glucose concentration and CP exists as the membrane localization of glucose transporter 1 may disappear by CP therapy.(14)

In our study, it seems that the high dose of dextrose administration was toxic in CP treated rats, and possibly administration of dextrose induces insulin secretion in non-diabetics rats which causes platinium accumulation in renal cortex.(18) Therefore, accumulation of CP in kidney promotes nephrotoxicity as shown by increase in kidney weight and Cr level increase in dextrose treated rats. Other study demonstrated that the serum level of insulin was increased after 3 days post CP injection, and CP-induced hyperglycemia and glucosuria precede CP induced acute renal failure.(24)

Conclusion

Collectively, our data not only did not support the nephro-protective role of dextrose hydration during CP therapy but also indicated that dextrose diets during CP therapy act as risk factor to promote CP-induced nephrotoxicity in female rats. Further studies are needed to find the exact mechanism.

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