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ORIGINAL ARTICLE

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Saline, mannitol, and furosemide hydration in acute cisplatin nephrotoxicity: a randomized trial

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Abstract *Objective*: To determine which hydration (saline, saline + mannitol, or saline + furosemide) is associated with least cisplatin nephrotoxicity. *Methods*: We randomized 49 women who received cisplatin (75 mg/m^2 every 3 weeks) into one of the three hydration arms. The 24-h creatinine clearance was measured before and on day 6 after cisplatin infusion. The patients of each arm received 2 l of saline hydration. In the saline + furosemide arm, 40 mg of furosemide was given after hydration. In the saline + mannitol arm, 50 g of mannitol was mixed with the cisplatin. *Results*: For the first cycle of chemotherapy, 15 women were randomized to saline, 17 to saline + furosemide, and 17 to saline + mannitol. For each group, the creatinine clearances before cisplatin infusion were (means ± SD, milliliters per minute) 84.5 ± 26.8, 82.5 ± 24.0 and 87.4 ± 25.6, and after cisplatin infusion were 79.1 ± 31.9, 68.7 ± 21.5, and 56.4 ± 22.9, respectively. The decreases in creatinine clearance were similar between the saline group and the saline + furosemide group ($P = 0.66$), but different between the saline + mannitol group and the saline group ($P = 0.02$) or the saline + furosemide group ($P = 0.02$). As each woman received multiple courses of cisplatin, 15 who received saline contributed 41 paired datasets, 17 who received saline + furosemide contributed 49 paired datasets, and 17 who received saline + mannitol contributed 36 paired datasets showed similar patterns. *Conclusions*: Hydration with saline or saline + furosemide appears to be associated with less cisplatin nephrotoxicity than saline + mannitol.

Keywords Hydration · Cisplatin nephrotoxicity · Mannitol · Furosemide

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Introduction

Cisplatin is a chemotherapy agent that has significantly improved the treatment of many malignancies including ovarian, germ-cell, small-cell lung, and head and neck cancers. Five recent randomized studies have shown that adding cisplatin to the standard radiation therapy in cervical cancer decreases the risk of death by 30–50% [1, 2, 3, 4, 5]. However, nephrotoxicity still severely limits cisplatin usage [6]. Within hours of cisplatin infusion, the somatic cisplatin concentration is much higher than in the liver and spleen [7]. This preferential "renal binding" is the presumed basis of renal toxicity. Renal blood flow is reduced by 33% and glomerular filtration rate is reduced by 78% 2 to 3 days after cisplatin infusion in dogs [8]. Cisplatin injures mitochondrial DNA at the cellular level more than nuclear DNA, since mitochondria lack the repair mechanism that exists in nuclear DNA [9]. These injuries result in renal mitochondrial dysfunction [10] and lead to a decline in adenosine triphosphate production. Loss of function impairs the cellular sodium-potassium pump, which then reduces proximal tubular sodium and water absorption. Since the largest concentration of renal mitochondria is in the third segment of the proximal tubule [11], the reduction in renal mitochondria leads to a decreased proximal tubule reabsorption rate [8]. Excess sodium and water that are not absorbed in the proximal tubule increase renal vascular resistance, which then decreases renal blood flow and glomerular filtration rate. After

cisplatin infusion in humans, the decrease in the glomerular filtration rate causes an increase in serum creatinine within 6 to 7 days. The serum creatinine levels remain elevated for 3 weeks [12].

A phase I study has shown cisplatin-induced nephrotoxicity to be one of the most serious dose-limiting factors [13]. However, a subsequent study has demonstrated that hydration with saline and mannitol reduces nephrotoxicity [12]. Mannitol, which causes osmotic diuresis, decreases the concentration of cisplatin in the urine. The lowered cisplatin concentration is thought to be a mechanism for reducing renal toxicity. Another study in patients with malignant melanoma has indicated that renal impairment is slightly lower when the cisplatin dose is accompanied by hydration and mannitol rather than by hydration alone. This study was conducted in the first cycle of cisplatin infusion and resulted in a lower level of renal toxicity (32% versus 39%). However, the renal protection was not as apparent in subsequent cycles [14]. In another study toxic doses of cisplatin (3 mg/kg) were evaluated in dogs. Renal toxicity was avoided with massive prehydration and with mannitol-induced diuresis [15]. A study of high-dose cisplatin (100 mg/m^2) together with mannitol or furosemide diuresis in 22 patients showed statistically similar nephrotoxicity: 28% and 19% decreases in creatinine clearance ($P > 0.25$), respectively [16]. It is interesting to note that mannitol may contribute to hypomagnesemia, since it increases magnesium excretion [17]. The protective effect of mannitol is still debatable [18, 19].

Studies involving furosemide diuresis used to decrease cisplatin-induced nephrotoxicity show conflicting results. Lehane et al. found an increased renal toxicity in rodents treated with cisplatin and furosemide [20]. Gehr et al. found that furosemide has no protective or harmful effect on cisplatin-treated rats [21]. Ward et al. [22] found a protective effect of furosemide in rats when given 30 min prior to (but not simultaneously with) cisplatin infusion by reducing urinary platinum concentration. Studies in humans comparing furosemide and mannitol have shown no nephrotoxicity differences as previously mentioned [16].

Although the exact mechanism of cisplatin-induced nephrotoxicity is unknown, hydration has been shown to reduce cisplatin toxicity [7]. In current clinical practice one of three types of hydration is used [23, 24]: saline, saline with mannitol, or saline with furosemide (Table 1). There has been no comparative study to determine which type of hydration results in lower renal toxicity in patients receiving cisplatin [7]. Therefore, the purpose of our study was to determine which hydration method results in the greatest reduction in acute nephrotoxicity in patients receiving cisplatin.

Methods

Adult women (18 to 80 years old) were recruited into this study if they were to receive 75 mg/m^2 of cisplatin alone or in combination with paclitaxel or 5-fluorouracil to treat gynecologic cancers. The exclusion criteria were as follows: use of nephrotoxic drugs (nonsteroidal antiinflammatory drugs, aminoglycosides, amphotericin B, or cephalosporins) or drugs that falsely elevate serum creatinine (sulfonamides); serum creatinine ≥2 mg/dl; diabetes or renal disease; poor performance status (Gynecologic Oncology Group score of 3 or 4); previous history of abdominal radiation; or any health condition that would be exacerbated by fluid hydration (e.g. heart failure or pulmonary edema). The Institutional Review Board at The University of Texas Medical Branch approved the protocol. All of the enrolled patients gave their written informed consent. The study was in accordance with the ethical standards for human experimentation established by the declaration of Helsinki of 1975, revised in 1983.

A complete history, physical examination, assessment of performance status/toxicity, serum creatinine, 24-h creatinine clearance, and other standard laboratory tests (metabolic panel, CA125 for patients with ovarian cancer) were done before each chemotherapy treatment. At each visit, the patient was instructed to collect urine over a single 24-h period starting at 7 a.m. and ending at 7 a.m. the next morning. The urine was continuously refrigerated. A special urine container was provided along with written instructions. These instructions were reinforced with a phone call prior to each urine collection, as well as during each clinic visit. Six days after cisplatin infusion, serum creatinine, 24-h creatinine clearance, other standard laboratory tests, and a physical examination were done.

Table 1 Various Gynecologic Oncology Group hydration protocols (*NS* normal saline)

Study no.[a]	Cisplatin (mg/m^2)	Type of solution[b]	Hydration		Comments
			Before cisplatin infusion	After cisplatin infusion	
85	50	1/2 or 1/4 NS	500 ml	500 ml	Mix 1 mg cisplatin in 1 ml sterile water
109	70	1/2 or 1/4 NS	1000 ml	1000 ml	Mix cisplatin in 1 l NS with 40 g mannitol
111	75	NS	Not stated	Not stated	Mix 1 mg cisplatin in 1 ml NS. May use diuretics
120	50	1/2 NS	1000 ml	500 ml	Mix 1 mg cisplatin in 1 ml water
152	75	NS	1000 ml in 4 h	1000 ml in 4 h	Mix 1 mg cisplatin in 1 ml sterile water
158	75	NS	1000 ml in 2–4 h	1000 ml in 2–4 h	Mix 1 mg cisplatin in 1 ml NS. May use diuretics
162	75	NS	1000 ml in 4 h	1000 ml in 4 h	Mix 1 mg cisplatin in 1 ml sterile water

[a]Gynecologic Oncology Group study number
[b]Type of hydration liquid used intravenously

Enrolled patients received chemotherapy with similar standard antiemetics and steroids (granisetron 10 μg/kg i.v. and dexamethasone 20 mg i.v. for 30 min before chemotherapy). Patients who received paclitaxel, in addition to their cisplatin, received cimetidine 300 mg i.v. and diphenhydramine 50 mg i.v. 30 min before chemotherapy. They were encouraged to increase their oral fluid intake before, during, and after cisplatin infusion. Once patient consent had been obtained, the patient was randomized into one of the three arms (Table 2) using a random-allocation table. Cisplatin was infused at a rate 0.5 mg/min. For safety reasons, any patient whose serum creatinine was 2 mg/dl or higher at any time during the study was removed from the study. Medical care was then transferred to her attending physician.

First cycle chemotherapy data were analyzed using the two-tailed Student's *t*-test. Categorical variables were analyzed using analysis of covariance. Using the three arms linear trend test, with alpha 0.05 and a power of 0.80, we estimated a sample size of 62 patients in each arm to find a 20% difference. Interim analysis at 25 patient accrual intervals (i.e. 25, 50, 75) were planned as a safety precaution. The relationship between serum creatinine and measured 24-h creatinine clearance was analyzed with Pearson's correlation coefficient.

Results

During an interim analysis of 50 patients, the saline + mannitol arm was found to be significantly more nephrotoxic. This finding was reported to the Institutional Review Board. This study was then closed prematurely in compliance with the Review Board recommendations. By the time the official decision to terminate the study had been made, an additional five patients had been enrolled in the study for a total of 55 patients. Six women could not collect their urine reliably after receiving cisplatin and were removed from the study (two from each hydration arm). The remaining 49 were randomized into one of the three arms: 15 in the saline arm gave 41 pairs of complete data (24-h creatinine clearance before and day 6 after cisplatin); 17 in the saline + furosemide arm gave 49 pairs of 24-h creatinine clearance data; and 17 in the saline + mannitol arm gave 36 pairs of 24-h creatinine clearance data. The characteristics of the patients are shown in Table 3.

The measured 24-h creatinine clearance before and after cisplatin infusion for the first chemotherapy course only is shown in Fig. 1. Thus, 49 women gave 49 pairs of data points. In this analysis, 15 were randomized to saline, 17 to saline + furosemide, and 17 to saline + mannitol. In the first cycle of chemotherapy, the 24-h creatinine clearances (means ± SD, milliliters per minute) in the saline, saline + furosemide and saline + mannitol groups were 84.5 ± 26.8, 82.5 ± 24.0 and 87.4 ± 25.6 before cisplatin infusion, and 79.1 ± 31.9,

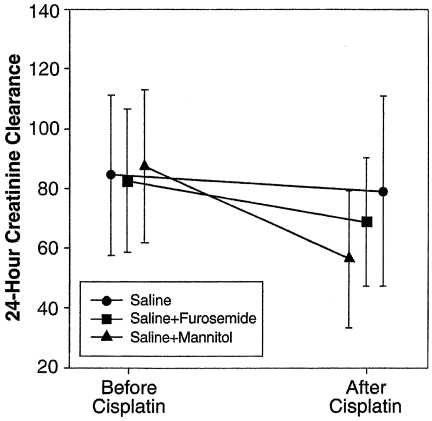

Fig. 1 Measured 24-h creatinine clearance before and after cisplatin infusion. These data and graphs were drawn only from the first course of chemotherapy (49 patients, 49 pairs of data). Each point represents the mean (*bars* ± SD)

Table 2 Hydration protocol (*NS* normal saline)

Type of hydration	Before cisplatin infusion	During cisplatin infusion	After cisplatin infusion
Saline	500 ml NS in 2 h	Mix cisplatin in 1000 ml NS	500 ml NS in 2 h
Saline + mannitol	500 ml NS in 2 h	Mix cisplatin in 1000 ml NS with 50 g mannitol	500 ml NS in 2 h
Saline + furosemide	500 ml NS in 2 h. 40 mg furosemide 30 min before cisplatin	Mix cisplatin in 1000 ml NS	500 ml NS in 2 h

Table 3 Characteristics of patients

Variable	Saline	Saline + furosemide	Saline + mannitol
Age (years) (mean ± SD)	49.0 ± 11.5	48.0 ± 8.2	43.7 ± 10.8
Weight (kg) (mean ± SD)	72.9 ± 18.3	71.8 ± 13.5	65.7 ± 10.7
Number of patients			
Recruited	17	19	19
With incomplete data	2	2	2
Analyzed	15	17	17
Chemotherapy cycles			
Total	41	49	36
Cisplatin alone	8	2	7
Cisplatin + 5-fluorouracil	9	10	11
Cisplatin + paclitaxel	24	37	18

68.7 ± 21.5 and 56.4 ± 22.9 after cisplatin infusion, respectively. The decrease in 24-h creatinine clearance was not different between the saline and saline + furosemide groups ($P = 0.66$). However, the decrease in 24-h creatinine clearance was markedly different between the saline + mannitol and saline groups ($P = 0.02$) and between the saline + mannitol and saline + furosemide groups ($P = 0.02$).

Figure 2 illustrates 24-h creatinine clearance before and after cisplatin infusion for the entire course of chemotherapy cycles. As each woman received multiple courses of cisplatin, they each contributed several pairs of 24-h creatinine clearance data for their assigned hydration method: 15 received saline and contributed 41 pairs of data, 17 received saline + furosemide and contributed 49 pairs of data, and 17 received saline + mannitol and contributed 39 pairs of data. The 24-h creatinine clearances (means ± SD, milliliters per minute) in the saline, saline + furosemide and saline + mannitol groups were 85.5 ± 24.2, 100 ± 21.3 and 82 ± 24 before cisplatin infusion, and 80.4 ± 33.5, 81.4 ± 23.3.1 and 60.6 ± 26.8 6 days after cisplatin infusion, respectively. The decrease in 24-h creatinine clearance was not different between the saline and saline + furosemide groups ($P = 0.65$). However, the decrease in 24-h creatinine clearance 6 days after cisplatin infusion was markedly different between the saline + mannitol and saline groups ($P = 0.04$) and between the saline + mannitol and the saline + furosemide groups ($P = 0.01$).

The 24-h creatinine clearance before cisplatin infusion in women who received saline + mannitol showed a cumulative decrease as they received several cycles of chemotherapy with saline + mannitol hydration (Figs. 1 and 2). The nephrotoxicity of cisplatin was more significant in women who received saline + mannitol than in women who received saline or saline + furosemide.

To confirm our study design of using 24-h measured creatinine clearance instead of serum creatinine or calculated creatinine clearance, we determined the degree of correlation between serum creatinine and 24-h creatinine clearance, and found a poor correlation (Pearson's correlation coefficient −0.52). The calculated 24-h creatinine clearance using the Cockcroft-Gault method also tended to overestimate the measured 24-h creatinine clearance (Pearson's correlation coefficient 0.62). Despite these discrepancies, a similar trend of declining creatinine clearance 6 days after cisplatin infusion continued when the glomerular filtration rate was estimated using serum creatinine or the Cockcroft-Gault method (Table 4).

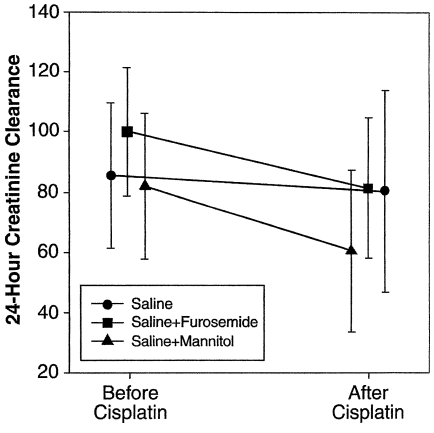

Fig. 2 Measured 24-h creatinine clearance before and after cisplatin infusion. These data and graphs were drawn from all chemotherapy cycles combined (49 patients, 126 pairs of data). Each point represents the mean (*bars* ± SD). The median cumulative cisplatin dosages (mg/m^2) for normal saline hydration, saline + furosemide hydration and saline + mannitol hydration are 219.6 (range 75–900), 229.7 (range 75–600) and 168.8 (range 75–600), respectively

Discussion

Our data suggest that mannitol hydration is associated with more nephrotoxicity than hydration with either saline alone or saline + furosemide. This basic information is crucial, since cisplatin continues to be one of the most commonly used chemotherapy agents with dose-limiting nephrotoxicity. It is now a part of the standard chemoradiation treatment for advanced cervical cancer. Furthermore, in studies of the relative nephrotoxicity of cisplatin (carboplatin versus cisplatin, efficacy of amifostine), mannitol hydration has been used [25, 26]. Our findings suggest a new paradigm that mannitol may contribute to cisplatin-related nephrotoxicity.

We had several choices in estimating glomerular filtration rate as an index of renal impairment: serum creatinine, inulin clearance, measured 24-h creatinine clearance, calculated 24-h creatinine clearance, and ^{51}Cr-EDTA. We elected to use 24-h creatinine clearance as the most cost-effective compromise in measuring glomerular filtration rate. Serum creatinine, although easy to obtain, has been known to be elevated only in the late course of renal impairment and has been determined to be an inadequate measure of glomerular filtration rate

Table 4 Calculated creatinine clearance and serum creatinine before and after cisplatin infusion. Data are presented as means ± SD

Hydration type	Creatinine clearance (ml/min)[a]			Serum creatinine (mg/dl)		
	Before cisplatin	After cisplatin	*P* value (two-tailed)	Before cisplatin	After cisplatin	*P* value (two-tailed)
Saline + mannitol	100.91 ± 28.4	87.49 ± 32.25	< 0.001	0.77 ± 0.17	0.95 ± 0.34	< 0.002
Saline + furosemide	106.85 ± 18.07	99.94 ± 18.92	< 0.005	0.73 ± 0.09	0.81 ± 0.16	< 0.001
Saline	103.88 ± 34.4	96.33 ± 36.21	0.06	0.84 ± 0.13	0.93 ± 0.3	0.03

[a]Calculated by the Cockcroft-Gault method

[27]. Serum creatinine does not usually become abnormal until the glomerular filtration rate has been reduced by 50%. Inulin has the characteristics of an ideal glomerular filtration rate marker because it is freely filtered at the glomerulus but is not absorbed or secreted by the tubule. However, measurement of inulin clearance is cumbersome and clinically impractical. The ^{51}Cr-EDTA clearance measurement has the highest correlation with glomerular filtration rate [28], but it is costly and takes 1 to 3 h per scan. At The University of Texas Medical Branch in Galveston, it costs $729 per renal scan. The laboratory cost of 24-h creatinine clearance is $47.

We used a total of 2 l of normal saline for each patient. This amount of hydration was adapted from various Gynecologic Oncology Group studies (Table 1). This approach was taken to simulate common clinical practice; therefore, the results of this study are applicable to clinical practice. In maintaining consistency to make our study applicable in general practice, we used serum creatinine in the inclusion and exclusion criteria and removal from the study. Many older studies of cisplatin nephrotoxicity have been criticized for using serum creatinine as end-points of the study, which prompted us to use measured creatinine clearance in the analysis of the study results.

Although our sample size was relatively small compared to other randomized trials, we found statistically significant differences. Our Institutional Review Board terminated the study for ethical reasons and a statistically significant finding. We complied and closed the study, realizing that we risked a type I error and would have preferred a P value of 0.005 for early termination. A possible weakness of our study was our dependence on the subjects to collect their urine correctly. Intensive teaching and regular reinforcement of proper urine collection may improve compliance but may not absolutely remove the concern for accuracy.

Our study showed an unexpected finding that is contrary to the common clinical practice of using mannitol diuresis with hydration to reduce cisplatin nephrotoxicity. We hope our results will encourage others to confirm our findings in a larger study and to evaluate other methods of reducing cisplatin toxicities (gastrointestinal toxicity, neurotoxicity, or ototoxicity) with saline hydration compared with mannitol hydration.

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