Nephroprotective Effects of Hydration with Magnesium in Patients with Cervical Cancer Receiving Cisplatin

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Abstract. *Aim: The present study aimed to assess the efficacy of 15 mEq magnesium supplied as part of a prehydration regimen in preventing cisplatin-induced nephrotoxicity in patients undergoing therapy with cisplatin-alone (40 mg/m^2/week) for cervical cancer. Patients and Methods: We studied 28 patients with cervical cancer. This prospective cohort study compared nephrotoxicity in patients who received hydration with and without magnesium sulfate (Mg-hydration group, n=14; non- Mg-hydration group, n=14). Results: Baseline characteristics, stage of cervical cancer, cisplatin dose and renal function did not differ significantly between the two groups. The serum creatinine level significantly increased from 0.58 to 0.75 mg/dl, and the estimated glomerular filtration rate significantly decreased from 85.1 to 66.5 ml/min by chemotherapy in the non-Mg-hydration group. In contrast, these levels did not change significantly in the Mg-hydration group. Conclusion: A magnesium dose of 15 mEq was found to provide nephroprotective effects among patients with cervical cancer undergoing chemotherapy with cisplatin alone.*

Cervical cancer is the second most common cancer in Japanese women. Cervical cancer morbidity and mortality are increasing in young people. The majority of patients with advanced-stage disease, including Federation Internationale de Gynecologie et de Obstetrique (FIGO) stage IIb and above, or patients with a high risk of recurrence with early-stage disease are treated with definitive concurrent chemoradiotherapy (CCRT) (1, 2). CCRT has been reported to improve progression-free survival and overall survival more effectively than radiation therapy-alone for FIGO stages Ib to IVa, and thus CCRT is currently the standard treatment for locally advanced cervical cancer (1, 2). CCRT regimens typically comprise either cisplatin alone or cisplatin combined with fluorouracil (1, 2). Cisplatin alone (40 mg/m^2/week) is administered as CCRT at Aichi Medical University Hospital, Japan.

Cisplatin administration is limited by nephrotoxicity, the dose-limiting toxicity of this agent, and damage due to nephrotoxicity becomes clinically problematic in 28-42% of patients who receive cisplatin (3, 4). Cisplatin alone (40 mg/m^2/week) as CCRT can be administered at a lower dose per unit time than other regimens, given its high dose intensity. Cisplatin-induced nephrotoxicity on treatment with cisplatin alone occurs at an incidence of 15.7% (5), which is lower than that of other regimens, but can cause irreversible side-effects that must be prevented during chemotherapy (6, 7).

The pathophysiological mechanisms of renal injury are not fully understood, but it is generally thought that the proximal renal tubule is damaged by cisplatin accumulation in renal tubular epithelial cells, leading to renal dysfunction. Hydration is the standard approach to prevent cisplatin-induced nephrotoxicity, as it increases the volume of urine and thus reduces the concentration of cisplatin and its contact time with the tubular epithelium (6, 7). Despite efforts to provide hydration in order to prevent cisplatin-induced nephrotoxicity, some patients still present clinical symptoms of renal dysfunction.

Hypomagnesaemia is one potential cause of renal dysfunction and thus represents an intervention target (8, 9). Among patients receiving cisplatin, 40% or more develop hypomagnesaemia (10, 11). Yokoo *et al*. proposed that hypomagnesaemia up-regulates the expression of renal organic cation transporter 2 (OCT2), which controls cisplatin transport into kidney cells (12). This would increase cisplatin accumulation in renal tissue, leading to cisplatin-induced nephrotoxicity (13). Magnesium-containing hydration is recommended in the National Comprehensive Cancer Network (NCCN) chemotherapy

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Table I. *Hydration protocol used for patients in the non-Mg-hydration and Mg-hydration groups at Aichi Medical University Hospital (chemotherapy regimen of cisplatin alone).*

	Non-Mg-hydration group			Mg-hydration group		
		Dose	Duration		Dose	Duration
Pre-hydration						
Day 0	Lactate Ringer's solution	1000 ml	12 h	Lactate Ringer's solution	1000 ml	12 h
				Magnesium sulfate	5 ml	
Day 1	Lactate Ringer's solution	1000 ml	6 h	Lactate Ringer's solution	1000 ml	6 h
				Magnesium sulfate	10 ml	
	0.9% Saline	50 ml	15 min	0.9% Saline	50 ml	15 min
	Granisetron	1 mg		Granisetron	1 mg	
	Dexamethasone	9.9 mg		Dexamethasone	9.9 mg	
	0.9% Saline	500 ml	1 h	0.9% Saline	500 ml	1 h
	Cisplatin	40 mg/m^2		Cisplatin	40 mg/m^2	
Post-hydration						
	Lactate Ringer's solution	500 ml	2 h	Lactate Ringer's solution	500 ml	2 h
Days 2 and 3	Lactate Ringer's solution	1000 ml	4 h	Lactate Ringer's solution	1000 ml	4 h
				Magnesium sulfate	5 ml	
	0.9% Saline	50 ml	15 min	0.9% Saline	50 ml	15min
	Dexamethasone	6.6 mg		Dexamethasone	6.6 mg	

order templates which include cisplatin (recommended dose, 8 mEq) (14) and Up to Data (recommended dose, 16 mEq) (18). Hydration solutions supplemented with magnesium was found to reduce cisplatin-induced nephrotoxicity in several clinical trials (16-18). However, the dose of magnesium of each hydration solution differed across the various reports, ranging from 8 to 80 mEq as pre-hydration, and thus the adequate dose required for preventing cisplatin-induced nephrotoxicity remains unclear (14-19). In addition, the preventive effects of magnesium on cisplatin-induced nephrotoxicity in patients with cervical cancer receiving cisplatin alone have not been examined. We determined that magnesium dose of prehydration was 15 mEq by reference to Up to Date (18), and started hydration with magnesium in patients receiving cisplatin regimen at Aichi Medical University Hospital in July 2012.

The present study was an open-label, non-randomized, historically-controlled study conducted to evaluate the effects of hydration supplemented with 15 mEq magnesium administered as pre-hydration in patients with cervical cancer receiving cisplatin alone.

Patients and Methods

Study participants. The present study was a single-center, prospective, open-label, non-randomized, historically controlled study conducted at our Institution, and targeted an experimental cohort (Mg-hydration group) and a retrospective control group (non-Mg-hydration group). Study participants received CCRT as primary therapy between January 2010 and October 2014.

Eligibility criteria were as follows: age <75 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1, cervical cancer stage I-IV, adequate bone marrow function, renal function [serum creatinine (Scr) <upper limit of the normal value and creatinine clearance (Ccr) >50 ml/min], and liver function [total bilirubin <1.5 mg/dl and transaminase <100 IU/l]. Patients with tumor infiltration into the ureter during treatment were excluded from the study. The following variables were recorded for each patient: age (years), body surface area (BSA), body mass index (BMI), histological diagnosis, PS according to the ECOG scale, disease stage, cisplatin dose, number of chemotherapy cycles, baseline renal function, and infusion volume. We also recorded nephrotoxicity risk factors such as diabetes and hypertension for each patient.

Study approval was obtained from the president of the Aichi Medical University Hospital, Aichi, Japan (approval number: 13-102). The Institutional Review Board decided to exempt this study from the usual review process.

Treatment. Chemotherapy was administered as a 1-hour infusion of intravenous cisplatin (40 mg/m^2), one day prior to radiotherapy. Chemotherapy treatment was repeated weekly, typically with the standard number of six chemotherapy cycles. All patients were treated with external beam radiotherapy (EBRT) 10 MeV by LINAC. Patients with positive vaginal mucosal surgical margins also received high-dose-rate intracavitary brachytherapy (HDR-ICBT) in addition to EBRT. EBRT (1.8 Gy/fraction) was delivered via anteroposterior and posteroanterior parallel ports to the entire pelvic field 5 days/week, for a total dose of 50.4 Gy. HDR-ICBT was delivered once weekly in a single dose of 4-5 Gy at point A,

Table II. *Patient characteristics*.

Characteristic	Non-Mg-hydration group (n =14)	Mg-hydration group (n = 14)	*p*-Value
Age years	52.2 (32-71)	58.2 (40-70)	0.21
BSA, m^2	1.45 (1.28-1.69)	1.47(1.22-1.65)	0.33
BMI, kg/m^2	20.3 (16.4-24.5)	21.1 (15.0-26.4)	0.49
Stage			
I	3	4	0.88
II	8	6	
III	2	2	
IV	1	2	
Histology			
Squamous cell carcinoma	11	12	0.38
Adenocarcinoma	3	1	
Large cell carcinoma	0	1	
PS			
0	13	14	0.33
1	1	0	
Dose of cisplatin, mg	55.0 (40-63)	57.1 (50-61)	0.76
No. cycles			
4	1	1	
5	4	2	0.68
6	9	11	
Delivered dose intensity,mg/m^2	33.2 (23.1-39.6)	37.2 (32.4-40)	0.11
Baseline renal function			
Serum creatinine, mg/dl	0.58 (0.47-0.68)	0.56 (0.40-0.69)	0.50
eGFR, ml/min	85.1 (69-108)	85.8 (65-137)	0.89
Ccr, ml/min	87.7 (55-120)	87.9 (60-120)	0.91

BSA, Body surface area; BMI, body mass index; PS, performance status; eGFR, estimated glomerular filtration rate; Ccr, creatinine clearance (Cockcroft-Gault). Data are numbers or the mean (range). No significant differences were observed between non-Mg and Mg groups.

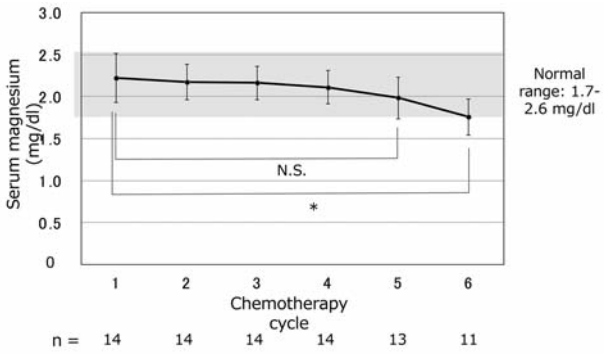

Figure 1. *Serum magnesium levels during each chemotherapy cycle in the Mg-hydration group. *Significant difference ($p<0.05$). N.S.: Not significant.*

which Point A is a hypothetical point that is located 2 cm above the cervical os (opening of the cervix) and 2 cm lateral to the central axis of the uterus, following EBRT. The total ICBT dose was 15-20 Gy.

As pre-hydration, cisplatin was dissolved in 500 ml of normal saline solution and infused throughout a program of enforced diuresis of 2500 ml of fluids (lactate Ringer's solution). Urine flow was established at rates of at least 100 ml/h for two days following cisplatin administration. If the urine flow rate dropped below 100 ml/h, an additional infusion solution was administered. If the additional infusion solution failed to increase the urinary flow, 20 mg furosemide was administered. Mannitol was not administered.

As post-hydration, 500 ml, 1000 ml, and 1000 ml of intravenous infusion fluid (lactate Ringer's solution) were added on days 1, 2, and 3, respectively. Beginning in July 2012, a modified hydration protocol which included magnesium sulfate was used (Table I). As pre-hydration, 15 mEq of magnesium sulfate was infused, and a daily dose of 5 mEq of magnesium sulfate was infused on days 2 and 3.

Study design. In July 2012, the hydration protocol used by our hospital Department of Obstetrics and Gynecology was modified to incorporate magnesium sulfate, with the intent to prevent nephrotoxicity in patients receiving cisplatin-based chemotherapy. Cisplatin-induced nephrotoxicity was evaluated in patients who received magnesium-infused hydration (Mg-hydration group: received hydration between July 2012 and October 2014) and compared to that in patients who had received hydration without magnesium (non-Mg-hydration group: received hydration between January 2010 and June 2012).

Cisplatin-induced nephrotoxicity was evaluated by measuring renal function [Scr, Ccr, and estimated glomerular filtration rate (eGFR)] during the period of chemotherapy administration. Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) criteria were also assessed for each patient (20).

Scr levels were measured enzymatically. Ccr was calculated using the Cockroft-Gault formula: Ccr=140–[age (years)]×weight (kg)×0.85/72/Scr (mg/dl). eGFR was calculated as follows: $eGFR=194\times Scr^{-1.094}\times age^{-0.287}\times 0.739$.

RIFLE criteria are widely used in cases involving acute nephrotoxicity (20). The Common Terminology Criteria for Adverse Events (CTCAE) classifies renal dysfunction only as an elevation of Scr, and does not refer to Ccr or GFR values. As the RIFLE criteria define nephrotoxicity according to Ccr and GFR values in addition to Scr, they were selected for the present study. RIFLE criteria define 'Risk' (Class R) as a proportional increase in Scr of more than 50% or a decrease in Ccr of less than 25% relative to baseline after cisplatin administration. In addition, "Injury" (Class I) is defined as a proportional increase in Scr of more than 100% or a decrease in Ccr of less than 50% relative to baseline after cisplatin administration. Each patient was classified according to RIFLE criteria, which we used as one measure of cisplatin-induced nephrotoxicity.

Beginning in July 2012, routine measurements of serum magnesium levels were obtained before each chemotherapy cycle as a way to monitor its dynamics following cisplatin administration.

Statistical analyses. R Version 2.14.2 (The R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses. Disease stage, histological diagnosis, PS, number of chemotherapy cycles, and RIFLE criteria were compared using Fisher's exact test. Other patient demographic data and infusion volume were compared

Table III. *Comparison of cisplatin-induced nephrotoxicity between the non-Mg-hydration group (n=14) and Mg-hydration group (n=14) before and after chemotherapy. We defined after chemotherapy as worst renal function in all chemotherapy cycles. Class R (risk) was defined as a proportional increase in serum creatinine (Scr) >50% or a decrease in creatinine clearance (Ccr) <25% relative to baseline, following cisplatin administration. Class I (injury) was defined as a proportional increase in Scr >100% or decrease in Ccr <50% relative to baseline following cisplatin administration.*

	Non-Mg-hydration group (n =14)		*p*-Value	Mg-hydration group (n = 14)		*p*-Value
	Before	After		Before	After	
Scr, mg/dl	0.58±0.07	0.75±0.15	<0.05	0.57±0.08	0.61±0.15	0.35
eGFR, ml/min	85.1±11.9	66.5±16.7	<0.05	85.8±19.3	80.8±18.3	0.27
RIFLE criteria						
Class R, n (%)	7 (50.0)			1 (7.1)		<0.05
Class I, n (%)	3 (21.4)			0 (0)		0.22

Data are expressed as mean ±s.d. eGFR, Estimated glomerular filtration rate; RIFLE criteria, Ratios of Risk, Injury, Failure, Loss, and End-stage kidney disease criteria (20).

using the Mann-Whitney U-test. The paired *t*-test was used to compare baseline values with worst renal function. The Wilcoxon's signed-rank test was used to compare serum magnesium levels before and after treatment. All reported *p*-values were two-sided, with a value of $p<0.05$ considered statistically significant.

Results

Data for 28 patients with cervical cancer (Mg-hydration group, n=14; non- Mg-hydration group, n=14) were included in the analysis. Tumor infiltration into the ureter was noted in one patient, who was excluded from the analysis. Patient characteristics showed no significant group-dependent differences (Table II). None of the patients in either group presented with diabetes mellitus or hypertension. Completion rates for six chemotherapy cycles were 64.3% and 78.6% for the Mg and non- Mg-hydration groups, respectively. The median cisplatin delivered dose intensity was 38.0 (range=30.3-42.3) mg/m^2/ week in the Mg-hydration group and 33.2 (range=23.2-39.6) mg/m^2/week in the non-Mg-hydration group. One patient in the non-Mg-hydration group discontinued chemotherapy due to renal toxicity, and thus only completed the radiation protocol. No treatment-related deaths occurred.

Baseline renal function showed no significant group-dependent differences (Table II). Comparison of baseline values with the worst renal function following chemotherapy in both groups indicated a significant change in the non-Mg-hydration group before and after chemotherapy, but not in the Mg-hydration group (Table III). Specifically, relative to baseline, patients in the non- Mg-hydration group showed increased Scr from 0.58 to 0.75 mg/dl and decreased eGFR levels from 85.1 to 66.5 ml/min after chemotherapy. Ccr levels also decreased by the end of chemotherapy (data not shown). According to RIFLE criteria, a significantly lower percentage of patients in the Mg-hydration group were in Class R (risk) relative to that in the non-Mg-hydration group (Mg-hydration group=7.1%; non-Mg-hydration group=50%; $p=0.03$). The percentage of patients in Class I (injury) did not differ significantly by group (Mg-hydration group=0%; non-Mg-hydration group=21.4%; $p=0.22$) (Table III). Of the seven patients who were classified in RIFLE criteria in both groups, five (74.1%) in the non- Mg-hydration group developed irreversible nephrotoxicity.

Infusion volumes on post-chemotherapy days 0 and 2 were greater in the non-Mg-hydration group than in the Mg-hydration group (Table IV). Serum magnesium levels during chemotherapy in the Mg-hydration group declined during chemotherapy, and most cases showed a significant decrease during the last chemotherapy period, relative to that of the first ($p=0.01$; Figure 1). Serum magnesium levels of one patient dropped to 1.4 mg/dl, which was below the normal range, but this patient did not develop cisplatin-induced nephrotoxicity.

Discussion

Even when the standard hydration treatment to prevent cisplatin-induced nephrotoxicity is provided, patients undergoing cisplatin chemotherapy can still develop renal dysfunction. Recommendations from the NCCN (recommended dose=8 mEq) and Up to Date (recommended dose=16 mEq) indicate the need for magnesium in the hydration solution in order to prevent cisplatin-induced nephrotoxicity (14, 15). However, to date, the specific dose of magnesium considered adequate for preventing cisplatin-induced nephrotoxicity has not been determined. In addition, this has not been reported for weekly treatments of cisplatin (40 mg/m^2). The present study revealed that Scr levels in the non-Mg-hydration group increased significantly with cisplatin chemotherapy, whereas no change was observed in patients who received prehydration with 15 mEq of magnesium (Mg-hydration group). A similar result was observed for

Table IV. *Volume of infusion each day and in total.*

Mean volume of infusion (range), ml	Non-Mg-hydration group (n =14)	Mg-hydration group (n = 14)	*p*-Value
Day 0	1,792 (0-2,000)	1,131 (0-2,000)	<0.05
Day 1	3,094 (2,150-3,100)	2,326 (1,550-3,550)	<0.05
Day 2	2,272 (1,050-3,100)	1,618 (1,550-2,600)	<0.05
Day 3	1,802 (0-3,100)	1,517 (1,050-2,100)	0.27
Total†	8,960 (5,250-12,250)	6,592 (5,150-9,550)	<0.05

†Total volume of infusion. Data are numbers or the mean (range).

eGFR, in that eGFR decreased significantly with chemotherapy in the non-Mg-hydration group, but did not significantly decrease in the Mg-hydration group. We assessed the validity of cisplatin-induced nephrotoxicity using RIFLE criteria and found a much lower incidence of nephrotoxicity in the Mg-hydration group than in the non-Mg-hydration group. This indicates that magnesium in the hydration protocol has a nephroprotective effect for patients receiving cisplatin alone for cervical cancer. None of the patients in the Mg-hydration group discontinued chemotherapy because of renal dysfunction, whereas one patient in the non-Mg-hydration group did. As cisplatin-induced nephrotoxicity can cause irreversible damage in many patients, this is an important issue to address, and could yield important clinical benefits. Infusion volume in the non-Mg-hydration group was higher than that in the Mg-hydration group, likely because patients in the non-Mg-hydration group showed occasional decreases in hourly urine flow due to cisplatin-induced nephrotoxicity. These patients were given additional infusion solution to address this. We surmise that these decreases in hourly urine flow may be considered a useful measure for detecting cisplatin-induced nephrotoxicity.

A retrospective study by Yoshida *et al*. found that cisplatin-induced nephrotoxicity decreased significantly when patients receiving more than 60 mg/m^2 cisplatin as a monthly dose were also given 8 mEq magnesium (16). While our results were consistent with these, that study did not measure serum magnesium levels. We found that serum magnesium levels could be maintained in the normal range by administering 15 mEq of magnesium during chemotherapy. However, serum magnesium levels gradually decreased with repeated chemotherapy in patients receiving cisplatin. We speculate that magnesium administration at a dose of 8 mEq would increase the incidence of hypomagnesaemia in patients, given our present results. In a randomized controlled trial by Bodnar *et al*., patients undergoing cisplatin chemotherapy for ovarian cancer were administered intravenous magnesium sulfate (5 g, or roughly 40 mEq) as pre-hydration (17). They found that serum magnesium levels measured during each period of chemotherapy did not differ significantly until the last period. Based on our findings, a magnesium dose lower than 40 mEq may have been possible. However, increasing the dose towards the last cycle of chemotherapy, when significant reductions in serum magnesium levels were noted, may be useful.

The present study determined that by using a hydration protocol with 15 mEq magnesium as pre-hydration can have important and beneficial implications in patients with cervical cancer who are receiving cisplatin-alone for chemotherapy. Future studies, such as a dose-finding study, are required to identify the adequate magnesium dose required to provide maximum nephroprotective effects. Post-hydration magnesium has been administered orally and intravenously, and two randomized controlled trials have been conducted to examine oral magnesium administration (17, 18). We chose intravenous administration on or after day 2 (5 mEq each on days 2 and 3), as orally-administered magnesium would be poorly absorbed by the gastrointestinal tract (21). The efficacy of post-hydration magnesium is currently unclear, and future studies should be conducted to assess its necessity.

Given the relatively small and non-randomized study population, large-scale, double-blind, and randomized studies are needed to confirm the utility of hydration with magnesium. Others have reported that intermediate-grade nephrotoxicity is difficult to identify using Scr as a parameter, and thus other urinary markers such as N-acetyl-beta-glucosaminidase or cystatin C may be useful to more accurately assess the degree of cisplatin-induced nephrotoxicity.

In conclusion, we found that a magnesium dose of 15 mEq provided nephroprotective effects in patients with cervical cancer undergoing chemotherapy with cisplatin alone. We recommend that all patients receiving cisplatin chemotherapy undergo hydration supplemented with magnesium during each chemotherapy cycle.

Conflicts of Interest

The Authors declare no conflicts of interest.

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