Protective effect of magnesium preloading on cisplatin-induced nephrotoxicity: which dose is more suitable?

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Abstract. – **OBJECTIVE:** Cisplatin is a widely used and potent cytotoxic chemotherapy agent, but its nephrotoxicity is a significant limiting side effect. Various premedication approaches have been implemented to preserve renal function, including magnesium (Mg) preloading. However, the optimal Mg dosage is still unknown. Our study aimed to assess the protective effects of different Mg doses as premedication in cisplatin-based chemoradiotherapy for patients with local/locally advanced cervical and head-neck cancers.

PATIENTS AND METHODS: This retrospective, multicenter study involved premedication with saline infusion containing potassium chloride and magnesium sulfate ($MgSO_4$) for all patients before cisplatin treatment. Patients were divided into two groups: 12 mEq $MgSO_4$ (low-dose Mg preload group, low-Mg) and 24 mEq $MgSO_4$ (high-dose Mg preload group, high-Mg). Renal function was evaluated using serum creatinine (sCr, mg/dl) and estimated glomerular filtration rate (eGFR, ml/min). Acute kidney injury (AKI) was defined per the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Renal outcomes and efficacy were compared between the groups.

RESULTS: In the low-Mg group (n = 159), sCr levels were significantly higher compared to baseline, various weeks during treatment, and at the 1st, 3rd, 6th, and 12th months post-treatment ($p < 0.001$). In the high-Mg group (n = 128), no significant changes were observed during treatment and at 1st, 3rd, and 12th months post-treatment ($p > 0.05$). A significant reduction in mean sCr level from baseline to 6 months was noted in the high-Mg group ($p < 0.001$). eGFR values are generally correlated with sCr levels. AKI occurred in 21 (13.2%) and 22 (17.7%) patients in the low-Mg and high-Mg groups, respectively ($p = 0.292$). There was no difference in progression-free or overall survival between the groups.

CONCLUSIONS: We clearly demonstrated that saline hydration with 24 mEql MgSO4 supplementation before cisplatin treatment has a better renal protective effect than 12 mEql MgSO4 without reducing efficacy, especially in patients with local/local advanced cervical and head-neck cancer receiving cisplatin with concurrent radiotherapy.

Key Words:
    Acute kidney injury, Cisplatin, Magnesium preloading, Nephrotoxicity.

Introduction

Cisplatin is a valuable and potent cytotoxic chemotherapy agent, widely used in daily oncology practice for various malignancies. Ototoxicity, nephrotoxicity, peripheral neuropathy, severe nausea and vomiting, and myelosuppression are common and well-known side effects of cisplatin treatment[1,2]. Renal tubular dysfunction and a cumulative impairment in kidney function, as manifested by a decline in the glomerular filtration rate and an increase in serum creatinine (sCr), are some of the most critical toxicities. Nephrotoxicity appears to be a clinical problem in a significant proportion of cases of patients treated with cisplatin in clinical practice. Although reported at various rates, generally, dose-dependent and cumulative nephrotoxicity due to cisplatin can

be seen in approximately 15% to 40% of cases[3,4]. Cisplatin-induced nephrotoxicity can manifest not only as acute and subacute kidney injury or chronic kidney disease but also through notable electrolyte imbalances, particularly hypomagnesemia and hypokalemia[5,6].

The pathogenesis of cisplatin-induced nephrotoxicity may result from multiple intracellular effects, including the direct toxicity of cisplatin accumulation in the proximal tubular epithelial cells, inflammatory effects of cisplatin with increasing reactive oxygen species and other inflammatory mediators, the activation of mitogen-activated protein kinase. As a result of all these factors, apoptosis and necrosis develop in proximal tubular epithelial cells, leading to hypomagnesemia, hypokalemia, and a decrease in renal functions[3,5-7]. On the other hand, hypomagnesemia itself enhances cisplatin-induced nephrotoxicity in addition to the direct cytotoxic damage of cisplatin to proximal tubular epithelial cells[8]. From another perspective, as mentioned above, diarrhea, nausea, and vomiting are frequently side effects of cisplatin treatment. As a result of these side effects, many patients may also experience magnesium (Mg) deficiencies, which can increase their susceptibility to renal damage. For these reasons, monitoring renal functions and Mg levels during cisplatin treatment is very important[3].

Cisplatin use is generally limited to patients with an estimated glomerular filtration rate (eGFR) > 60 mL/min. Due to its significant side effect, which poses considerable limitations during treatment, various premedication approaches have been employed over the years in clinical trials[7] and daily practice to preserve renal functions. These protective approaches can be summarized as pre-treatment hydration, potassium and Mg replacement, and forced diuresis with mannitol, particularly in patients receiving high doses of cisplatin (> 100 mg/m²)[9]. Specifically examining Mg supplementation, as discussed in this article, studies[3,7,10-12] with different cancer groups and varying Mg doses (typically 8 to 16 mEq) indicate that premedication regimens containing Mg generally reduce cisplatin-associated renal damage compared to regimens without Mg.

Despite the well-known renal protective effect of Mg replacement prior to cisplatin treatment, there is still no clear consensus or guideline recommendation on which patient group should receive Mg replacement and the ideal Mg dose due to the lack of well-designed studies. The optimal Mg amount for use in concurrent cisplatin with radiotherapy remains unknown. This study aims to evaluate the protective effects of different Mg replacement doses as premedication in a cisplatin-based chemoradiotherapy regimen for patients with local/locally advanced cervical and head-neck cancers.

Patients and Methods

This study was designed as a retrospective, multicenter investigation to explore the protective effect of various doses of Mg administered as premedication before cisplatin on drug-related renal toxicity in patients with local/locally advanced cervical and head-neck cancers receiving concurrent radiotherapy. In our study conducted in three cancer centers, patients whose diagnosis and treatment process were completed between June 2010 and May 2023 were retrospectively evaluated. Patients over 18 years old with pathologically confirmed local/local advanced cervical and head and neck cancer with various histopathologies were included in the study. Patients who received adjuvant chemoradiotherapy after surgery or patients who received definitive chemoradiotherapy were included in the study. Patients with known brain or other distant metastases, those treated with other cytotoxic agents without cisplatin, patients with known renal disease, those with an initial eGFR < 60 mL/min, and patients whose treatment methods, including antiemetic therapies and Mg preloading, were altered during cisplatin therapy were excluded from this study.

Cisplatin was administered to each patient in 1,000 cc saline concurrently with radiotherapy for at least one cycle. It was given over a period exceeding 90 minutes in varying doses and regimens, based on patient characteristics and clinicians' preferences, at experienced centers. As premedication before cisplatin treatment, saline infusion containing potassium chloride (KCl) and magnesium sulfate ($MgSO_4$) was administered to all patients in 1,000 cc for 2 hours. Antiemetics consisted of 5-HT3 antagonists (ondansetron, granisetron, or palonosetron) and dexamethasone prophylaxis, and pheniramine was also given before cisplatin treatment.

Patients' baseline demographic and clinical characteristics before cisplatin treatment were recorded from hospital databases. Additionally, sCr and eGFR values were documented pre-cis-

platin treatment, during treatment, and at 1, 3, 6, and 12 months post-treatment, as available due to the study's retrospective design. It was observed that all centers administered the same dose of 20 mEq KCl as premedication before each cycle. Despite using regimens with varying doses of $MgSO_4$, most clinicians were noted to administer $MgSO_4$ at doses of 12 mEq and 24 mEq. During the retrospective review, applica-

tions where the exact dose of $MgSO_4$ was not clearly identified or differed from the specified doses were not included in our study's analysis. Then, patients were divided into two groups before analysis: patients who were treated with 12 mEq $MgSO_4$ (low-dose Mg preloading group, low-Mg) and patients who were treated with 24 mEq $MgSO_4$ (high-dose Mg preloading group, high-Mg). The patients included in the study
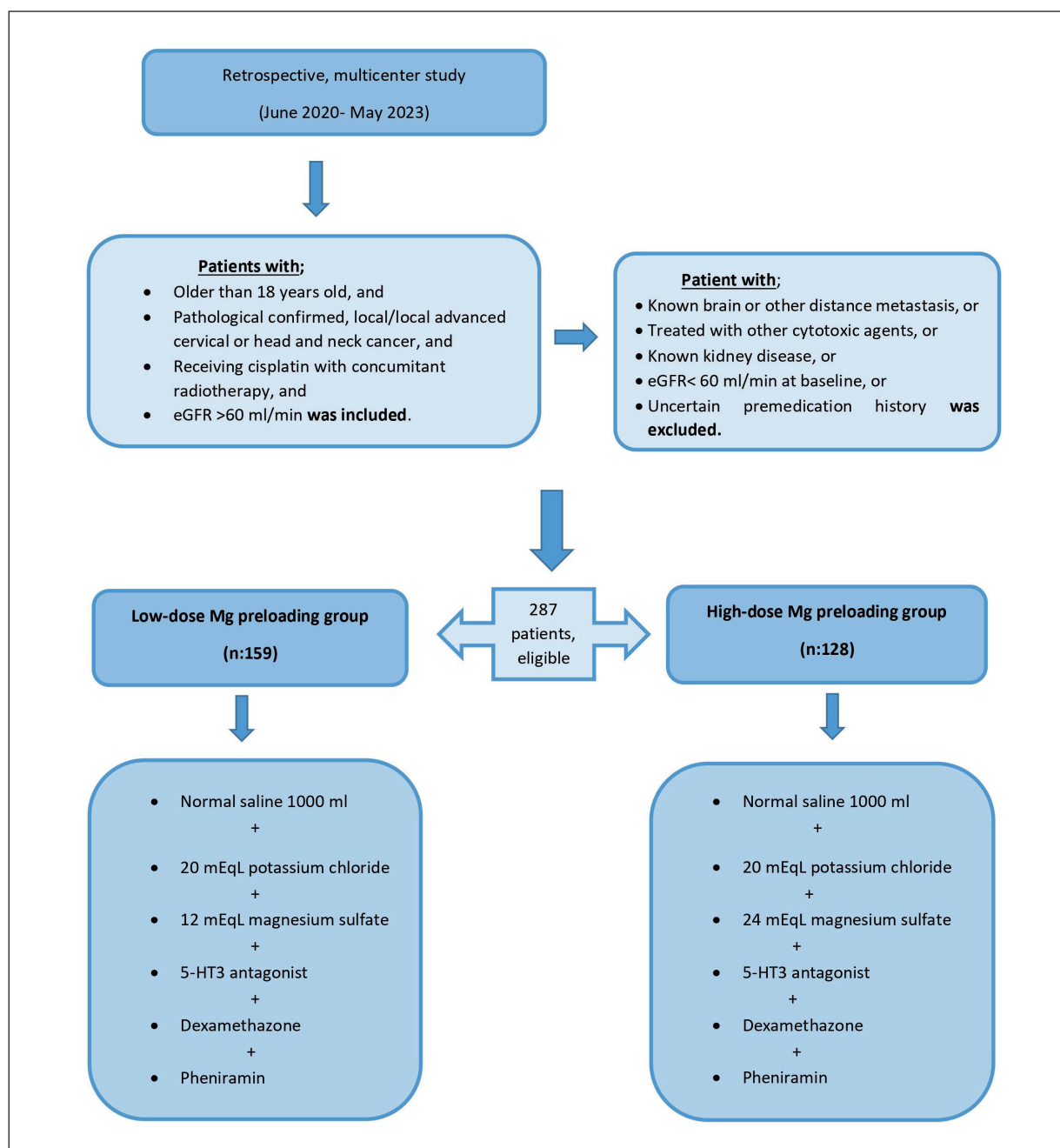

Figure 1. The summary of the patients included in the study and their treatment schemes.

and their treatment schemes are summarized in Figure 1.

Renal function was evaluated using sCr (mg/dl) and eGFR (ml/min). eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI, 2021) formula, incorporating creatinine, age, and sex. Due to the retrospective design, we assessed changes in sCr and eGFR during and after treatment. In this study, we also recorded acute kidney injury (AKI) occurring during the cisplatin regimen, defined as grade 3 or higher according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0[13].

This study was designed and conducted by Good Clinical Practice and the Declaration of Helsinki. It was approved by the University of Health Sciences, Antalya Training and Research Hospital Clinical Research Ethics Committee (Approval date/No.: 24/08/23/11/12).

Statistical Analysis

Statistical analyses were performed using SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as n and % for categorical variables and Mean±SD for continuous variables. Data were assessed for normality using the Kolmogorov-Smirnov test. Independent t-tests were used for binary group comparisons. Paired Sample tests were utilized to compare repeated measures during and after treatment. The Kaplan-Meier method was employed to compare overall survival (OS) and progression-free survival (PFS) across different clinical parameter groups. A significance level of $p < 0.05$ was considered statistically significant.

Results

A total of 287 patients diagnosed with local or locally advanced cervical or head and neck cancer, meeting the study criteria, underwent concurrent chemoradiotherapy with cisplatin and were enrolled in the investigation. The mean age of the patient cohort was 61.92 ± 12.66 years. Among the participants, 133 (46.3%) were diagnosed with cervical cancer, while 154 (53.7%) had head and neck cancer. The distribution between the low-Mg and high-Mg groups revealed 159 (55.4%) and 128 (44.5%) patients, respectively. The use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), known to adversely affect renal functions, as well as non-steroidal anti-inflammatory drugs (NSAIDs) and iodinated contrast media, was well distributed among the groups, and no statistical difference was found between the groups. In addition, no statistically significant difference was found between the total cisplatin doses (mg/m²) administered between the groups ($p = 0.587$). The baseline mean sCr levels were 0.74 ± 0.19 mg/dl and 0.81 ± 0.17 mg/dl in the low-Mg and high-Mg groups, retrospectively ($p = 0.001$). The baseline eGFR levels were 97.3 ± 18.3 ml/min and 89.3 ± 19.6 ml/min in the low-Mg and high-Mg groups, retrospectively ($p < 0.001$). The baseline mean serum magnesium levels were similar between the groups ($p = 0.155$). The baseline sociodemographic characteristics and important biochemical values of the patients and the distribution between the groups are summarized in detail in Table I.

During chemoradiotherapy treatment, the low-dose Mg group exhibited a notable increase in mean sCr values compared to pre-cisplatin baseline levels. Specifically, at the 1st, 2nd, 3rd, 4th, and 5th weeks, the recorded values were 0.82, 0.84, 0.85, 0.86, and 0.90 mg/dl, respectively, indicating a statistically significant elevation ($p < 0.001$ for all). In contrast, the high-dose Mg group demonstrated stability in mean sCr values compared to the initial average value. At the 1st, 2nd, 3rd, 4th, and 5th weeks, the respective values were 0.80, 0.82, 0.79, 0.81, and 0.77 mg/dl, with no significant deviation from baseline values ($p > 0.05$ for all). In the low Mg group, a trend of decreasing eGFR was observed as weeks progressed during treatment compared with pre-cisplatin baseline values. Mean eGFR values were significantly lower at the 1st, 2nd, 3rd, 4th, and 5th weeks, respectively recorded as 89.7, 88.0, 86.6, 87.1, and 83.8 ml/min ($p < 0.001$ for all). In contrast, in the high Mg group, the mean eGFR values for the 1st, 2nd, 3rd, 4th, and 5th weeks were 92.3, 94.1, 92.6, 90.8, and 94.5 ml/min, respectively. A significant inverse relationship was observed only between the baseline eGFR values and those in the 5th week ($p = 0.02$). The results were similar in the other weeks, and no significant decrease in eGFR was observed ($p > 0.05$ for all other weeks). Changes in mean sCr and eGFR values over weeks during chemoradiotherapy treatment were demonstrated in Figure 2.

Post-treatment assessment of renal functions, initiated one month after the completion of chemoradiotherapy, revealed noteworthy out-

Table I. Comparison of sociodemographic and clinical characteristics data with Mg groups.

Variables	Total n = 287	Mg Low n = 159	Mg High n = 128	*p*
Gender, n (%)				**0.001**[a]
Male	108 (37.6)	74 (46.5)	34 (26.6)	
Female	179 (62.4)	85 (53.5)	94 (73.4)	
Comorbidity, n (%)				0.149[a]
Absent	165 (72.7)	100 (77.5)	65 (66.3)	
HT	45 (19.8)	22 (17.1)	23 (23.5)	
DM	17 (7.5)	7 (5.4)	10 (10.2)	
Ecog, n (%)				**< 0.001**[a]
0	30 (10.5)	16 (10.1)	14 (10.9)	
1	224 (78.0)	138 (86.8)	86 (67.2)	
2	33 (11.5)	5 (3.1)	28 (21.9)	
Cancer, n (%)				**< 0.001**[a]
Head and neck cancer	154 (53.7)	111 (69.8)	43 (33.6)	
Cervical cancer	133 (46.3)	48 (30.2)	85 (66.4)	
Head and neck subtype, n (%)				0.201[b]
Nasopharynx	26 (18.6)	17 (16.7)	9 (23.7)	
Oropharynx	28 (20.0)	24 (23.5)	4 (10.5)	
Hypopharynx	1 (0.7)	0 (0)	1 (2.6)	
Larynx	72 (51.4)	52 (51)	20 (52.6)	
Other	13 (9.3)	9 (8.8)	4 (10.5)	
Histological diagnosis, n (%)				**< 0.001**[b]
Squamous cancer	249 (86.8)	150 (94.3)	99 (77.3)	
Adenocancer	22 (7.7)	6 (3.8)	16 (12.5)	
Adenosquamous cancer	8 (2.8)	3 (1.9)	5 (3.9)	
Other	8 (2.8)	0 (0)	8 (6.3)	
Type of treatment, n (%)				0.081[b]
Definitive	212 (73.9)	111 (69.8)	101 (78.9)	
Adjuvant	75 (26.1)	48 (30.2)	27 (21.1)	
ACE or ARB, n (%)				0.420[a]
Absent	216 (75.5)	123 (77.4)	93 (73.2)	
Present	70 (24.5)	36 (22.6)	34 (26.8)	
NSAID, n (%)				0.131[a]
Absent	239 (83.9)	127 (80.9)	112 (87.5)	
Present	46 (16.1)	30 (19.1)	16 (12.5)	
Contrast exposure, n (%)				0.318[a]
Absent	190 (66.4)	101 (63.9)	89 (69.5)	
Present	96 (33.6)	57 (36.1)	39 (30.5)	
Total cisplatin dose (mg/m²), n (%)				0.587[b]
< 100	8 (2.9)	6 (3.8)	2 (1.6)	
100-200	147 (51.2)	81 (50.9)	66 (51.6)	
> 200	132 (46.0)	72 (45.3)	60 (46.9)	
Progression, n (%)				0.758[a]
Absent	240 (83.6)	132 (83)	108 (84.4)	
Present	47 (16.4)	27 (17)	20 (15.6)	
Mortality, n (%)				0.493[a]
Alive	201 (70.0)	114 (71.7)	87 (68)	
Deceased	86 (30.0)	45 (28.3)	41 (32)	
Age, Mean ± SD	61.92 ± 12.66	61.33 ± 12.73	62.66 ± 12.59	0.376[c]
BMI (kg/m²), Mean ± SD	27.29 ± 5.85	28.36 ± 6.20	25.97 ± 5.10	**0.001**[c]
sCr (mg/dL), Mean ± SD	0.77 ± 0.18	0.74 ± 0.19	0.81 ± 0.17	**0.001**[c]
Mg (mg/dL), Mean ± SD	2.07 ± 1.11	1.97 ± 0.20	2.17 ± 1.56	0.155[c]
BUN (mg/dL), Mean ± SD	15.10 ± 6.54	15.75 ± 7.19	14.31 ± 5.58	0.058[c]
K (mmol/L), Mean ± SD	4.38 ± 0.38	4.51 ± 0.39	4.35 ± 0.36	0.187[c]
eGFR (ml/min), Mean ± SD	93.78 ± 19.34	97.38 ± 18.37	89.31 ± 19.64	**< 0.001**[c]

[a]Pearson's Chi-square test, [b]Fisher's Exact test, [c]Independent *t*-test, *p* < 0.05 statistically significant. Mg: magnesium, HT: hypertension, DM: diabetes mellitus, ACE: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blockers, NSAID: non-sterodial anti-inflammatory drugs, BMI: body-mass index, sCr: serum creatinine, K: serum potassium, eGFR: estimated glomerular filtration rate.
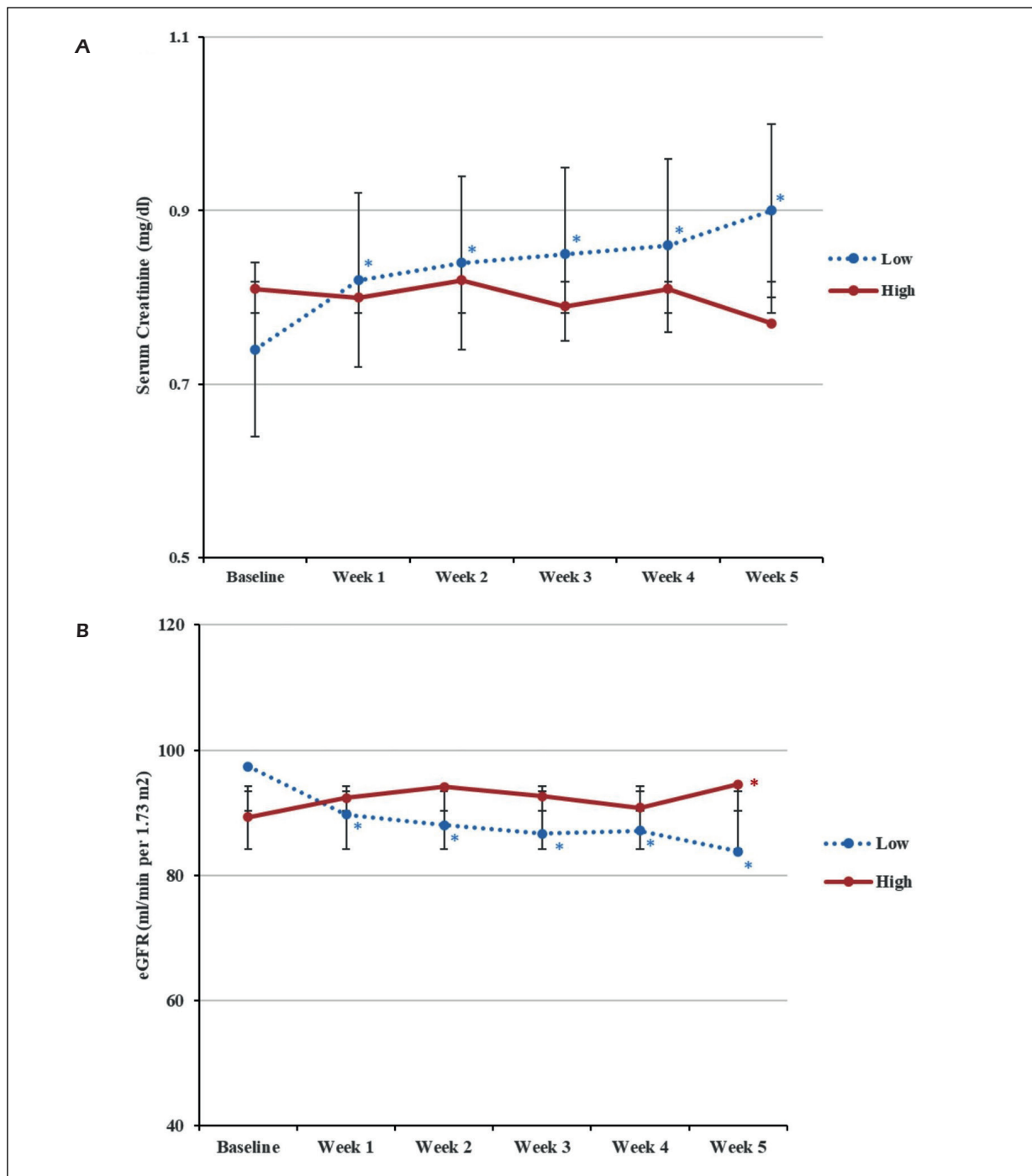
Figure 2. Mean serum creatinine (**A**) and mean estimated glomerular filtration rate (**B**) over weeks during chemoradiotherapy treatment according to the low-dose and high-dose Mg preloading groups. (*$p < 0.05$ compared to baseline value with paried samples test).

comes. In the low-Mg group, mean sCr values at 1 month, 3 months, 6 months, and 12 months were statistically significantly elevated compared to baseline levels. Specifically, these values were recorded as 0.93, 0.91, 0.88, and 0.89 mg/dl, respectively ($p < 0.001$ for all). In contrast, within the high-Mg group, mean sCr values at 1 month, 3 months, 6 months, and 12 months were determined as 0.81, 0.78, 0.79, and 0.85 mg/dl, respectively. Upon individual

scrutiny, no statistically significant differences were identified between the 1-month, 3-month, 12-month, and baseline values ($p > 0.05$ for all). Notably, a statistically significant reduction in mean sCr level between baseline and 6 months was observed in the high-Mg group ($p < 0.001$). In the low Mg group, the mean eGFR values at 1, 3, 6, and 12 months were found to be statistically significantly lower than the baseline value, recorded as 80.9, 81.5, 83.0, and 82.8 ml/min,

respectively ($p < 0.001$ for all). In contrast, the mean eGFR values at 1, 3, 6, and 12 months in the high-dose Mg preloading group were 91.3, 93.3, 91.0, and 88.1 ml/min, respectively. No statistically significant difference was found between the average baseline eGFR and the 1, 3, 6, and 12-month average eGFR values ($p > 0.05$ for all). Changes in mean sCr and eGFR values over months after completion of chemoradiotherapy treatment were shown in Figure 3.
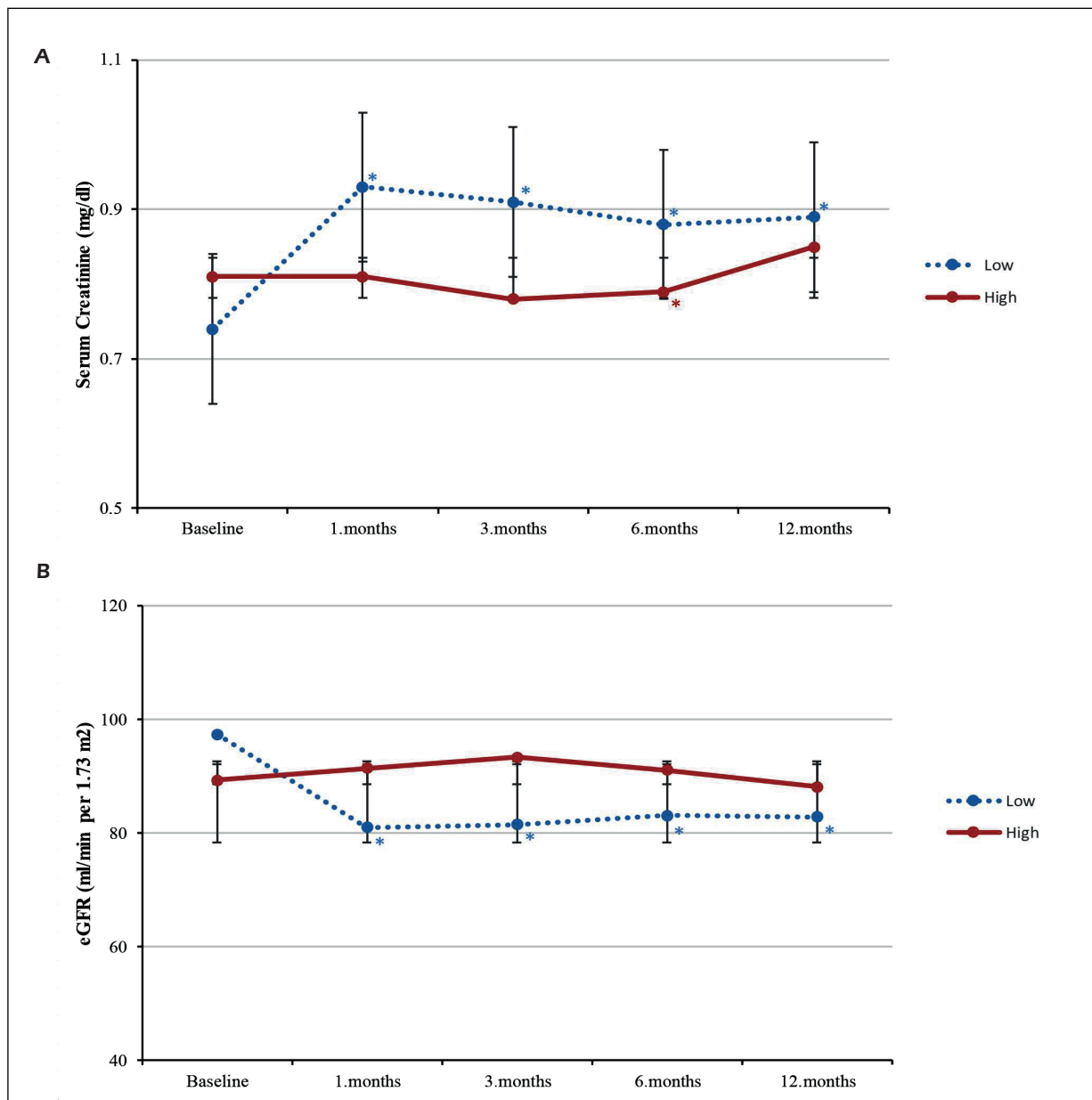

Figure 3. Mean serum creatinine (**A**) and mean estimated glomerular filtration rate (**B**) over months after chemoradiotherapy treatment according to the low-dose and high-dose Mg preloading groups. (*$p < 0.05$ compared to baseline value with paried samples test).

As mentioned above, we evaluated AKI emerging during cisplatin regimen, defined as grade 3 or higher according to CTCAE version 5.0. Among all patients receiving cisplatin with chemoradiation, AKI developed at various weeks during treatment in 43 of 287 patients (15.2%). The incidence of AKI was 21 (13.2%) in the low-dose Mg preloading group and 22 (17.7%) in the high Mg group, with no statistical difference between the groups ($p = 0.292$). A detailed comparison of AKI across magnesium groups is presented in Table II.

Within the entire population, progression was observed in 47 (16.3%) patients, while 86 (29.9%) died from disease-related or other causes. Although median progression-free survival (PFS) was not reached in either the low or high Mg groups, the 2-year PFS rates were similar at 85.3% and 89.5%, respectively ($p = 0.449$). Similarly, median overall survival (OS) in the low Mg group was 82.1 months (95% CI, 64.0-100.3), and not reached in the high-Mg group. The 2-year OS rates were similar at 83.5% and 84.6%, respectively ($p = 0.892$).

Discussion

Cisplatin remains one of the most frequently used drugs in daily oncology practice, yet unfortunately, nephrotoxicity continues to be its most serious side effect. Due to this significant limitation during treatment, various premedication approaches, including magnesium supplementation, have been utilized over the years in clinical trials[7] and daily practice to preserve renal functions. Although the renal protective effect of pre-treatment Mg replacement is well-known, there is still no consensus or guideline recommendation on which patient group should receive Mg replacement and the ideal Mg dose. This study aims to evaluate the protective effects of different Mg replacement doses as premedication in cisplatin-based chemoradiotherapy regimen for patients with local/locally advanced cervical and head-neck cancers.

A total of 287 patients were included in the study, with 159 (55.4%) in the low-Mg group and 128 (44.5%) in the high-Mg group. The initial demographic characteristics of our patient population were generally similar across groups. The use of ACEIs or ARBs, NSAIDs, and iodinated contrast media known to affect renal functions adversely, was well-distributed among the groups with no statistical difference. Furthermore, no significant difference was found in total administered cisplatin doses (mg/m^2) between groups, making the comparative evaluation of renal functions between the two groups generally appropriate and reliable.

In this study, we investigated the determination of the ideal dose of Mg, which is now routinely used in premedication before cisplatin treatment, and differences between administering 12 mEqL (low-Mg group) and 24 mEqL (high-Mg group) in terms of renal outcome were examined. As mentioned above, in the high-dose Mg preloading group, no significant increase in sCr or decrease in eGFR was observed during treatment or in the measurements taken at different weeks post-treatment and up to 12 months. Conversely, a significant increase in sCr and a trend towards a decrease in eGFR were observed in the low Mg group. In the high-Mg group, eGFR increased in the 5th week of treatment compared to baseline. Additionally, the mean sCr was found to be lower than baseline values in the 6th month post-treatment. Numerous studies[3,7,10,12,14,15] have shown that adding various doses of MgSO$_4$ (8 to 20 mEqL) to routine saline infusion for premedication is generally more effective than not, though the ideal dose remains unknown. Muraki et al[10] designed a retrospective study with 50 patients with non-small cell lung cancer treated with cisplatin (75

Table II. Comparison of Mg Groups with AKI.

| Variables | Total n = 287 | Mg | | p |
		Low n = 159	High n = 128	
AKI, n (%)				0.292*
Absent	240 (84.8)	138 (86.8)	102 (82.3)	
Present	43 (15.2)	21 (13.2)	22 (17.7)	

*Pearson's Chi-square test. Mg: magnesium, AKI: acute kidney injury.

mg/m^2) and pemetrexed. Patients were divided into two groups: one treated with a hydration protocol containing normal saline and forced diuresis, and the other with a new hydration protocol including normal saline, magnesium (MgSO$_4$, 8 mEq), and forced diuresis. After one cycle, patients receiving Mg supplementation showed a significant increase in eGFR ($p = 0.0004$) and a decrease in sCr ($p = 0.0148$), indicating that the hydration protocol with Mg supplementation could prevent nephrotoxicity caused by cisplatin and pemetrexed without affecting treatment outcomes. In a prospective trial by Yamamoto et al[12], 28 cervical cancer patients undergoing therapy with cisplatin (40 mg/m^2/week) and concurrent radiotherapy were studied. Patients were divided into two premedication groups: a non-Mg-hydration group and an Mg-hydration group. In the non-Mg hydration group, cisplatin caused a significant rise in sCr from 0.58 to 0.75 mg/dl, and a significant decrease in creatinine clearance from 85.1 to 66.5 ml/min. Conversely, no significant changes were observed in these parameters in the Mg-hydration group. As a result of these studies[12], 15 mEq of Mg given as part of the prehydration regimen, with an additional 5 mEq administered over two days post-hydration, is shown to prevent cisplatin-induced nephrotoxicity in patients treated solely with cisplatin. Yoshida et al[3] conducted a retrospective study involving 496 patients with thoracic malignancies who received cisplatin at a dose of 60 mg/m^2. In patients who received Mg in their prehydration (n = 161), compared to those who did not (n = 335), a significantly lower incidence of grade 2 sCr elevation was observed both in the initial cycle and across all cycles ($p < 0.001$ for both). Multivariate analysis indicated that Mg supplementation significantly reduced the risk of nephrotoxicity by 3.8-fold during the first cycle ($p < .001$) and by 4.3-fold over all cycles ($p < .001$). The authors also claimed that Mg preloading had a preventive effect on cisplatin-induced nephrotoxicity. However, the appropriate dose for Mg preloading and the utility of Mg supplementation before and after cisplatin administration are still unclear. Recently, Suppadungsuk et al[7] presented a pilot prospective randomized control trial with 30 head and neck cancer patients. The two groups were compared for acute kidney injury, defined as a ≥ 0.3 increase in SCr from baseline to final sCr: in 30 head and neck cancer patients over 7-8 weeks, premedication consisted of intravenous 500 ml normal saline plus 20 mEq of KCl without Mg (control group) *vs.* the addition of an extra 16 mEq of MgSO$_4$ (magnesium preloading group) before weekly 40 mg/m^2 cisplatin. The magnesium-preloading regimen significantly showed a decreased incidence of acute kidney disease (6.7% for the Mg-preloading group *vs.* 46.7% for the control group, $p = 0.03$). Kimura et al[15] planned a retrospective study with 121 head and neck cancer patients who were treated with cisplatin and 5-fluorouracil. The authors demonstrated that an intravenous hydration regimen supplemented with MgSO$_4$ (20 mEql) prevented cisplatin-induced nephrotoxicity in head and neck cancer patients. To our knowledge, this is the first study in which Mg doses were directly compared to evaluate the protective effects of cisplatin nephrotoxicity. As shown by these reported studies[3,7,15], Mg supplementation is essential for reducing the risk of nephrotoxicity. Based on the results of this study involving a large number of patients, we suggest that adding 24 mEql MgSO$_4$ to saline before cisplatin treatment has a better renal protective effect compared to 12 mEql MgSO$_4$. This is particularly beneficial for patients with local or locally advanced cervical and head-neck cancer who are undergoing cisplatin treatment concurrently with radiotherapy, even though the study had a retrospective design.

In this study, AKI was defined as requiring hospitalization (grade 3 or above) according to CTCAE, version 5.0. It was observed that 43 of the 287 patients (15.2%) developed AKI during treatment in different weeks. The number of patients developing AKI was similar in both groups ($p = 0.292$). In general, the incidence of cisplatin-induced AKI is challenging to estimate due to the variabilities of patient populations and criteria of AKI[16,17]. Latcha et al[18] planned a study to evaluate renal outcomes of cisplatin with 821 patients with different tumor types. In this study, the authors defined AKI as an increase from the baseline creatinin of > 25% within 30 days after the first cycle of cisplatin. AKI occurred in 31.5% of patients.

While it is not suitable to offer and juxtapose precise epidemiological data due to variances in AKI definitions and patient demographics, our study suggests that likely owing to stricter criteria, AKI occurrence was lower among our patient cohorts.

Although our study was designed to evaluate toxicity, survival analyses were also performed. The 2-year PFS and OS rates were similar in both low-dose and high-Mg groups. Saito et al[19] planned a study with 58 head and neck cancer patients while receiving cisplatin, docetaxel, and 5-fluorouracil, and they showed that 20 mEqL Mg

premedication had a protective effect on kidney without affecting response rates. From a different perspective, it has been shown in a retrospective study written by Liu et al[20] that hypomagnesemia during treatment is prognostic of overall survival for patients with head and neck cancers who are receiving concurrent chemoradiation with cisplatin and/or carboplatin. More severe hypomagnesemia was found to be associated with shorter survival. Thus, in our current trial, while the risk of nephrotoxicity is reduced with high-dose $MgSO_4$ (24 mEqL) replacement compared with low-dose $MgSO_4$ replacement, it can be concluded that there is no change in survival and efficacy. Evaluation of efficacy and survival should be supported by prospective randomized studies.

Although this study, which had a high number of patients, had important results, this retrospectively planned study had some limitations. Firstly, although we evaluated the initial serum Mg levels and there was no statistical difference between the groups, we did not evaluate the association between cisplatin-induced nephrotoxicity and the serum or urinary Mg level due to retrospective design. A second limitation is our inability to perform a correlational assessment of the total dose of cisplatin (mg/m^2) with the body surface area of each patient despite no difference in the total cisplatin doses. Thirdly, due to the study's retrospective nature, there may be minor variations in fluid administration and duration before or after treatment, even though the planned volume and ratio of fluids in the protocol were the same. Lastly, as this study planned for renal outcomes, survival results should be carefully evaluated due to two different cancer groups, indeterminate stages, and heterogeneous patient populations.

Conclusions

We have clearly demonstrated that saline hydration supplemented with 24 mEq of $MgSO_4$ before cisplatin treatment offers a better renal protective effect than 12 mEq of $MgSO_4$ without reducing efficacy, especially in patients with local/locally advanced cervical and head-neck cancer receiving concurrent radiotherapy and cisplatin.

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