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Comparative Study of Different Doses of Magnesium sulfate as A Protective Agent in Cisplatin Induced Nephrotoxicity in Patients with Head and Neck Cancer Abstract

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Abstract

Background: *Head and neck cancer (HNC) are a collection of cancers that develop in the oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, salivary glands, or head and neck lymph nodes. The purpose of this investigation was to evaluate the potential advantages of magnesium (Mg) in cisplatin-induced nephrotoxicity prevention and to estimate the suitable dosage of Mg for patients had HNC.*

Methods: *This randomized, controlled, parallel, clinical study involved 100 patients had HNC, managed at Clinical Oncology Department Tanta University Hospital, Tanta, Egypt. According to randomization, patients were divided into 4 equal groups; group 1 (control group) received cisplatin, group 2 (8 Meq Mg) received cisplatin with hydration 8 Meq Mg, group 3 (16 Meq Mg) received cisplatin with hydration 16 Meq Mg and group 4 (24 Meq Mg) received cisplatin with hydration 24 Meq Mg.*

Results: *Multivariable Cox proportional hazards regression was conducted for variables that showed a significant association in univariable regression. Mg intake still showed better overall survival than group 1 after adjusting for previous smoking effect, where the adjusted HR was 0.361 (95% CI: 0.166 to 0.785; p = 0.010. The risk was still significantly higher among previous smokers compared to non-smokers, even after adjusting for the treatment effect (HR: 2.759; 95% CI: 1.254 to 6.070; p = 0.012).*

Conclusions: *Mg can be used as a protective agent in cisplatin induced nephrotoxicity as it decreases blood urea nitrogen, serum creatinine and increase eGFR compared to cisplatin alone regimen.*

Keywords: *Magnesium, Protective, Cisplatin, Induced Nephrotoxicity, Head and Neck Cancer.*

INTRODUCTION

Head and neck cancers (HNC) are a collection of cancers that develop in the oral cavity, pharynx, larynx, salivary glands, paranasal sinuses, nasal cavity, or head and neck lymph nodes [1]. HNC is the 7th prevalent malignancy globally, related to mortality rate of 300,000 deaths and approximately 600,000 cases reported yearly, particularly in developing countries [2-4]. Head and neck squamous cell carcinoma (HNSCC), arises from the mucosal lining epithelium of the upper aerodigestive tract, comprise over 90% of HNC [5]. Upper aerodigestive tract secondary tumor development in approximately 20% of oral SCC cases was reported [6].

kidneys are the primary site of cisplatin accumulation and excretion. It is possible for non-toxic blood levels to be toxic in the kidneys due to the fact that the drug's concentrations in the tubule epithelial cells are 5 times greater than those in the blood. The efficacy of treatment may be jeopardized by the restricted capacity to increase drug dosage due to dose-dependent renal toxicity [7]. The proximal tubule is the primary site of toxic effects, with the tubule epithelium cells on segment S-3 being particularly affected. Glomeruli and distal tubules are implicated at a later stage. Patients typically recover from acute drug toxicity, which is why chronic nephrotoxicity is uncommon. The majority of nephrotoxicity complications are acute kidney injury (AKI) and hypomagnesemia [8].

Magnesium (Mg) is capable of protecting the kidneys from the toxicity of cisplatin. Renal organic cation transporter 2 expression, which is up-regulated in hypomagnesemia and regulates the transport of cisplatin into kidney cells leads to decrease cisplatin-induced nephrotoxicity risk [9]. Hypomagnesemia itself enhances cisplatin-induced nephrotoxicity in addition to the direct cytotoxic damage of cisplatin to proximal tubular epithelial cells. From another perspective, as mentioned above, diarrhea, nausea, and vomiting are frequently side effects of cisplatin treatment [10].

A prevalent clinical symptom of platinum-induced nephrotoxicity and renal Mg wasting is hypomagnesemia. Post-sixth cycle of cisplatin treatment, hypomagnesemia prevalence has been estimated

to as high as 100%. Disappointingly, the conventional approach of administering intravenous Mg and oral Mg supplementation has failed to sustain Mg levels [11]. As demonstrated in a recent review of 229 patients had ovarian cancer, managed by carboplatin-based chemotherapy, hypomagnesemia was correlated with a shorter survival time, regardless extent of tumor reductive surgery or cancer stage [12].
Renal tubular platinum accumulation, tubular injury and oxidative stress are all exacerbated by Mg depletion, as evidenced by experimental models. Consequently, kidney function is diminished. Furthermore, Mg supplementation was found to alleviate renal tubular injury in a mouse model of Mg deficiency after both one and numerous doses of cisplatin [13].
Examining Mg supplementation, studies 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 owing to the scarcity of well-designed studies. The optimal Mg amount for use in concurrent cisplatin with radiotherapy remains unknown [13-15]. The preventive value of magnesium intake against cisplatin-induced nephrotoxicity in individuals with HNC has not been established in any study.
The purpose of study was to examine Mg value in cisplatin-induced nephrotoxicity prevention in patients had HNC to determine Mg dosage.

PATIENTS AND METHODS

This randomized, controlled, parallel, clinical study involved 100 patients with HNC with estimated glomerular filtration rate (eGFR) lower than 59 ml/min/1.73m^2, Eastern cooperative oncology group performance status (ECOG) higher than 2, managed at Clinical Oncology Department Tanta University Hospital, Tanta, Egypt.
The patient or their relatives provided written informed consent. The investigation was conducted following the approval of the Ethical Committee of Tanta University Hospitals (35629/8/22) and the registration of clinicaltrials.gov (ID: NCT05586009).
Exclusion criteria were pregnant or lactating women, patients with severe co-morbidity conditions just as cerebrovascular coma, ischemic heart diseases chronic renal diseases, with known hypersensitivity to any of the used drugs, other nephrotoxic drugs as aminoglycosides, contrast media and NSAID drug, and those with diabetes mellitus.

Randomization:

The sealed opaque envelope technique was employed to allocate participants to the treatment group, and randomization was conducted in accordance with computer-generated random number tables. The patients were categorized into 4 categories based on the randomization process:

- Group 1 (control group) (n=25): received cisplatin only.
- Group 2 (8 Meq Mg) (n=25): received cisplatin with hydration 8 Meq Mg intravenous infusion.
- Group 3 (16 Meq Mg) (n=25): received cisplatin with hydration 16 Meq Mg intravenous infusion.
- Group 4 (24 Meq Mg) (n=25): received cisplatin with hydration 24 Meq Mg intravenous infusion.

Every patient underwent a thorough history taking, general examination, and laboratory investigation, which included CBC, renal function testing (blood urea nitrogen (BUN), serum creatinine (sCr), BUN/SrCr ratio, and eGFR), serum electrolytes (Mg (pre/post-cisplatin), potassium, sodium, calcium, phosphate), liver function (ALT, AST, and alkaline phosphate), urinalysis, estimation of urinary neutrophil gelatinase associated lipocalin (NGAL), urinary kidney injury molecule-1 (KIM-1), serum malondialdehyde (MDA), and serum soluble Fasl preoperative and 5 days after last cisplatin dose. All parameters were measured before treatment, after treatment and at 7 cycles.

Intervention and hydration protocol:

All patients received a standardized hydration regimen before and after cisplatin. Pre-hydration involved administering 1000 mL of 0.9% saline solution for 2 hours before cisplatin infusion. Each group received the designated Mg sulfate dose as an intravenous infusion mixed in 500 mL of 0.9% saline over 60 minutes before cisplatin administration. Additional electrolyte supplementation with potassium chloride (20 mEq in 500 mL of 0.9% saline) was administered over 1 hour if serum potassium levels were low (<3.5 mEq/L). Some of cases received antiemetic prophylaxis included 5-HT3 receptor antagonists (ondansetron 8 mg IV or granisetron 1 mg IV), dexamethasone (8 mg IV), and neurokinin-1 receptor antagonists (aprepitant 125 mg orally on day 1, followed by 80 mg on days 2 and 3).

Cisplatin was administered at a dose of 40 mg/m² as a 2-hour IV infusion in 500 mL of 0.9% saline. To minimize nephrotoxicity, mannitol (12.5 g IV push) and furosemide (20 mg IV) were given before cisplatin to promote diuresis. Post-hydration included 2000 mL of 0.9% saline infused over 24 hours after cisplatin. Additional hydration adjustments were made based on urine output and renal function monitoring.

Sample collection and biomarker assessment:

Samples were collected at baseline, after each treatment cycle, and five days after last cisplatin dose. sCr and eGFR were calculated using the Chronic Kidney Disease Epidemiology Collaboration formula to evaluate renal function. Urinary Mg excretion was evaluated to determine renal Mg handling. The NGAL Rapid ELISA Kit (Bioporto, Denmark) was employed to measure urinary NGAL using an enzyme-linked immunosorbent assay (ELISA) technique.

Urinary KIM-1 was also assessed. Urine samples were collected at baseline, three months, and six months post-treatment, centrifuged at 716–2683×g for approximately 20 minutes, and stored frozen at -80°C until analysis using ELISA kits (Biont Human KIM-1 ELISA, SunRed Biotechnology, China). Serum MDA was measured to assess oxidative stress.

Blood samples were collected before any diagnostic procedures or treatments, processed, and analyzed using a spectrophotometric method (Spectrophotometer UV/Vis, Perkin Elmer, Lambda 25). Serum soluble Fas ligand (sFasL)) concentration was measured at baseline and and five days after last cisplatin dose. sFasL concentrations were quantified using a commercial Luminex screening assay on a Bio-Rad Bio-Plex 200 system.

OS was quantified as days between the initial chemotherapy administration and mortality date and PFS was from drug administration date to PD. Using the questionnaire developed by EORTC, QLQ-C30 version 3.0, and its module H&N35, QoL parameters were assessed [16].

The QLQ-H&N35 is a questionnaire that is specifically designed to meet HNC patients' needs. It comprises 35 items that are designed to assess health-related quality of life. It includes 11 single items (problems with teeth, sticky saliva, problems opening the mouth, dry mouth, cough, feeling ill, pain killers, nutritional supplements, feeding tube, weight loss, and weight gain) and seven scales (pain, swallowing, senses, speech, social contact, social eating and sexuality). Items 1 through 30 are evaluated on a four-point Likert scale: 1 represents "not at all," 2 represents "a little," 3 represents "quite a bit," and 4 represents "very much." Items 31-35 employ a response format of 'yes' (2) and 'no' (1). As all of the scales evaluate symptoms, scores that are higher are indicative of a reduced quality of life [17].

Outcome measure:

The primary outcome included the degree of renal function preservation across the different Mg supplementation groups. Nephrotoxicity was defined based on a ≤ 20% in eGFR from baseline and the incidence of AKI, classified according to Common Terminology Criteria for Adverse Events version 5.0 [10].

The secondary outcome included comparisons of electrolyte imbalances across groups, particularly hypomagnesemia and hypokalemia, cisplatin-induced nausea and vomiting incidence and severity and changes in NGAL, KIM-1, MDA, and sFasL levels across treatment cycles.

Statistical analysis:

Software SPSS v28 (IBM©, Armonk, NY, USA) was utilized for statistical analysis. The data distribution was checked for normality using the Shapiro-Wilks test and histograms. The quantitative parametric data was analyzed using an ANOVA (F) test with a Tukey post hoc test, and the results were shown as the mean and SD. For the purpose of comparing the same subjects across different conditions or time points, repeated measures ANOVA tests were employed. The Chi-square test was employed to analyze qualitative variables, and the results were presented as percentages and frequencies (%). A two-tailed P value less than 0.05 was used to determine statistical significance. The Kaplan-Meier curve demonstrated OS and progression-free survival. To find out how one (univariate) or more (multiple) independent variables relate to a dependent variable, utilize logistic regression for that.

RESULTS

An assessment of eligibility was conducted for 139 patients in this study. Twenty-four patients did not satisfy the criteria, and fifteen patients declined to participate. Out of the remaining 100 patients, four equal groups were randomly assigned (25 patients in each). All patients who were allocated were statistically analysed and followed up. **Figure 1**

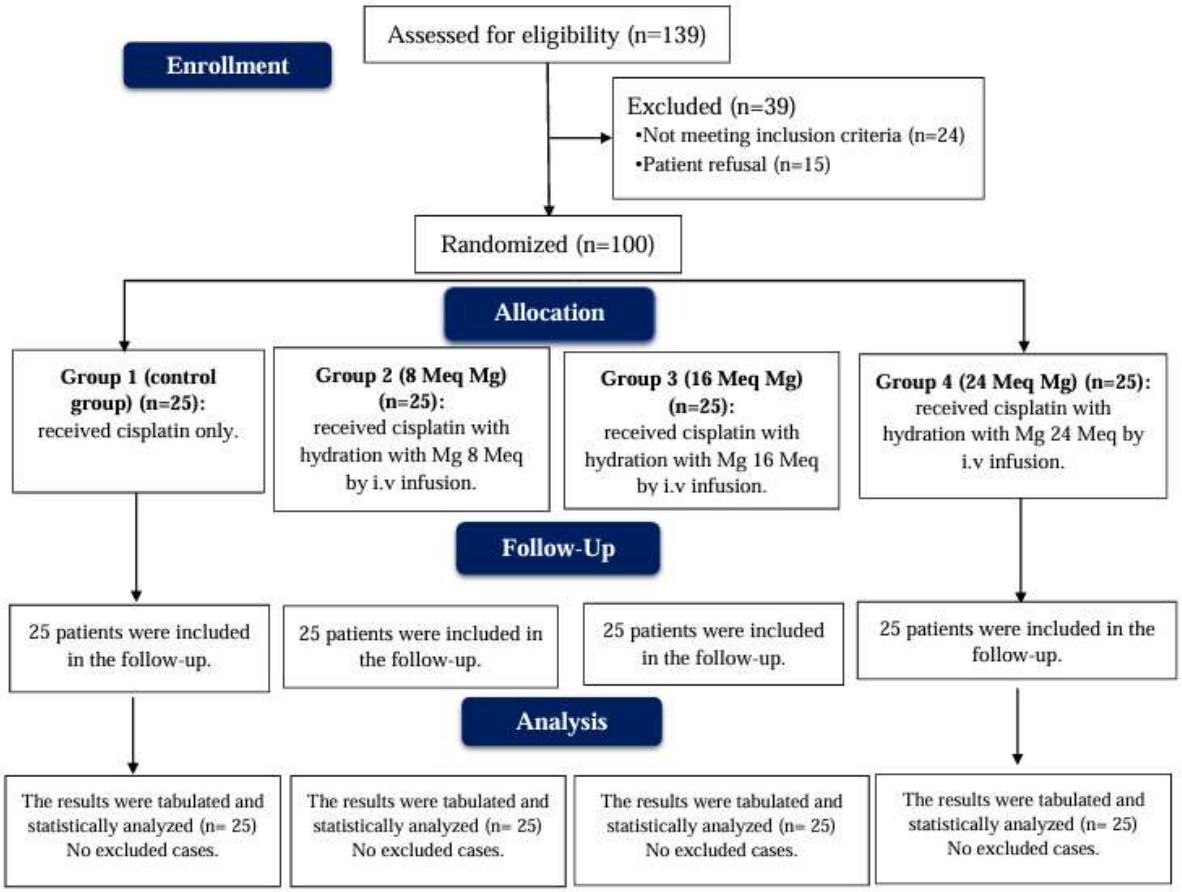


Figure 1: CONSORT flowchart of the enrolled patients

The baseline characteristics, including age, sex, weight, height, BMI, BSA, residence, and ECOG performance status, previous smoking and family history and regarding the anatomical site of HNC, the cisplatin dose/cycle, total Cisplatin dose and the total fluid volume were indifferent among the studied groups **Table 1**

Table 1: Baseline characteristics, anatomical site of head and neck cancer of the studied groups

		Total (n=100)	Group 1 (control group) (n=25)	Group 2 (Mg 8 Meq) (n=25)	Group 3 (Mg 16 Meq) (n=25)	Group 4 (Mg 24 Meq) (n=25)	P value
Age (years)		53.8 ± 9.4	55.96 ± 9.7	53.04 ± 9	52.6 ± 10.24	53.7 ± 8.78	0.644
Sex	Male	62 (62%)	14 (56%)	17 (68%)	16 (64%)	15 (60%)	0.837
	Female	38 (38%)	11 (44%)	8 (32%)	9 (36%)	10 (40%)	
Weight (Kg)		76.4 ± 8.52	75.6 ± 9.18	77.4 ± 7.57	74.4 ± 7.42	78 ± 9.72	0.427
Height (m)		1.7 ± 0.17	1.68 ± 0.05	1.67 ± 0.05	1.69 ± 0.04	1.66 ± 0.05	0.406
BMI (Kg/m^2)		27.3 ± 3.49	26.99 ± 4.06	27.66± 2.98	26.14 ± 2.6	28.25±3.93	0.166
BSA (m^2)		1.8 ± 0.11	1.74 ± 0.12	1.76± 0.13	1.75 ± 0.1	1.76 ± 0.1	0.874
Residence	Urban	57 (57%)	16 (64%)	13 (52%)	15 (60%)	13 (52%)	0.774
	Rural	43 (43%)	9 (36%)	12 (48%)	10 (40%)	12 (48%)	
ECOG performance status	0	60 (60%)	16 (64%)	12 (48%)	17 (68%)	15 (60%)	0.506
	1	40 (40%)	9 (36%)	13 (52%)	8 (32%)	10 (40%)	
Previous smoking		30 (30%)	10 (40%)	8 (32%)	4 (16%)	8 (32%)	0.306
Family history		4 (16%)	2 (8%)	3 (12%)	2 (8%)	4 (16%)	0.716
Anatomical site of cancer							

Nasopharynx	21 (21%)	6 (24%)	6 (24%)	3 (12%)	6 (24%)	0.834
Larynx	29 (29%)	5 (20%)	10 (40%)	7 (28%)	7 (28%)	
Oral cavity	23 (23%)	5 (20%)	4 (16%)	8 (32%)	6 (24%)	
Paranasal sinuses	7 (7%)	2 (8%)	1 (4%)	3 (12%)	1 (4%)	
Hypopharynx	20 (20%)	7 (28%)	4 (16%)	4 (16%)	5 (20%)	
Cisplatin dose						
Cisplatin dose/cycle	–	69.4 ± 4.6	70.6 ± 5.15	70.1 ± 4.18	70.2 ± 4.18	0.768
Total Cisplatin dose	–	486.1 ± 32.21	493.9± 36.04	490.6± 29.28	491.7 ± 29.23	0.847
Total fluid volume (L)	–	3.93 ± 0.05	3.95 ± 0.05	3.94 ± 0.05	3.94 ± 0.05	0.516

Data presents as mean ± SD or frequency (%). BMI: body mass index, BSA: Body Surface Area, ECOG: Eastern cooperative oncology group performance status. *: significant as P value ≤ 0.05.

sCr at end cycle was significantly lower in group 3 (Mg 16 Meq) and group 4 (Mg 24 Meq) compared to control group. eGFR at the end cycle was significantly higher in group 3 (Mg 16 Meq) and group 4 (Mg 24 Meq) than group1. There was no significant difference among the studied groups regarding the blood urea nitrogen level at baseline, after the 1st cycle, and at the end cycle. **Table 2**

Table 2: Kidney function tests of the studied groups

	Group 1 (control group) (n=25)	**Group 2 (Mg 8 Meq) (n=25)**	**Group 3 (Mg 16 Meq) (n=25)**	**Group 4 (Mg 24 Meq) (n=25)**	**P value**	**Post hoc**
Serum creatinine (mg/dL)						
At baseline	0.77 ± 0.11	0.75 ± 0.1	0.74 ± 0.1	0.73± 0.11	0.588	
After the 1st cycle	0.80 ± 0.11	0.79± 0.12	0.78 ± 0.1	0.77± 0.11	0.788	
At the end cycle	0.87 ± 0.15	0.82± 0.12	0.79± 0.11	0.78 ± 0.1	**0.043***	P1=0.220 **P2=0.029*** **P3=0.019*** P4=0.273 P5=0.204 P6=0.892
Blood urea nitrogen (mg/dL)						
At baseline	19.72 ± 2.49	19.8 ± 2.58	19.2 ± 2.31	20.24± 2.55	0.533	–
After the 1st cycle,	21.12 ± 2.47	19.6 ± 3.34	19.96±2.35	19.04 ± 2.67	0.058	–
At the end cycle	21.44 ± 2.29	19.8 ± 3.52	19.92±2.69	19.4 ± 2.65	0.063	–
eGFR (ml/min/1.73m2)						
At baseline	94.04±13.26	95.52± 18.26	98.08± 14.82	96.56±14.82	0.821	
After the 1st cycle	83.2 ± 12.88	87.9 ± 18.39	90.6 ± 14.74	91.3 ± 12.75	0.210	
At the end cycle	77.6 ± 11.23	84.8 ± 18.22	87.9± 10.71	89.6± 11.93	**0.011***	P1=0.097 **P2=0.002*** **P3=0.001*** P4=0.470 P5=0.280 P6=0.603

Data presents as mean ± SD. eGFR: Estimated glomerular filtration rate. *: significant as P value ≤ 0.05, P1: P value between group I & II, P2: P value between group I and III, P3: P value between group I & IV, P4: P value between group II & III, P5: P value between group II & IV, P6: P value between group III & IIV.

Urine NGAL/CR after the 1st cycle and at the end cycle was significantly lower in group 2 (Mg 8 Meq), group 3 (Mg 16 Meq) and group 4 (Mg 24 Meq) compared to group 1 (control group), was significantly

lower in group 3 (Mg 16 Meq) and group 4 (Mg 24 Meq) than group 2 (Mg 8 Meq) and was significantly lower in Mg 24 Meq group than group 3 (Mg 16 Meq). Urine KIM /Cr after the 1st cycle and at the end cycle was significantly lower in group 2 (Mg 8 Meq), group 3 (Mg 16 Meq) and group 4 (Mg 24 Meq) compared to group 1 (control group), was significantly lower in group 3 (Mg 16 Meq) and group 4 (Mg 24 Meq) than group 2 (Mg 8 Meq) and was significantly lower in group 4 (Mg 24 Meq) compared to group 3 (Mg 16 Meq). Serum-soluble FasL after the 1st cycle and at the end cycle was significantly lower in group 2 (Mg 8 Meq), group 3 (Mg 2 mg) and group 4 (Mg 24 Meq) compared to group 1 (control group), was significantly lower in group 3 (Mg 16 Meq) and group 4 (Mg 24 Meq) compared to group 2 (Mg 8 Meq). MDA after the 1st cycle was significantly lower in group 2 (Mg 8 Meq), group 3 (Mg 16 Meq) and group 4 (Mg 24 Meq) than control group, with no significant difference between the other groups and each other's. MDA at the end cycle was significantly lower in group 2 (Mg 8 Meq), group 3 (Mg 16 Meq) and group 4 (Mg 24 Meq) compared to group 1 (control group), was significantly lower in group 3 (Mg 16 Meq) and group 4 (Mg 24 Meq) compared to group 2 (Mg 8 Meq). **Table 2**

Table 3: Kidney injury biomarkers of the studied groups

	Group 1 (control group) (n=25)	Group 2 (Mg 8 Meq) (n=25)	Group 3 (Mg 16 Meq) (n=25)	Group 4 (Mg 24 Meq) (n=25)	P value	Post hoc
Urine NGAL/CR (ng/ml)						
At baseline	3.08 ± 0.82	3.03 ± 0.88	2.6 ± 0.74	2.99 ± 0.89	0.162	
After the 1st cycle	10.94± 5.15	7 ± 2.53	6.22 ± 2.05	4.87 ± 1.62	**<0.001***	**P1=0.001*, P2<0.001*, P3<0.001*,** P4=0.236 **P5=0.001* P6=0.013***
At the end cycle	28.53±14.84	13.45 ± 4.6	10 ± 3.34	7.59 ± 1.67	**<0.001***	**P1<0.001*, p2<0.001*, P3<0.001*, P4=0.004*, P5<0.001*, P6=0.002***
Urine KIM /Cr (ng/mg)						
At baseline	1.75 ± 0.45	1.61 ± 0.31	1.57 ± 0.41	1.54 ± 0.38	0.247	
After the 1st cycle	9.09 ± 1.82	6.23 ± 1.48	5.1 ± 1.14	3.62 ± 1.01	**<0.001***	**P1<0.001*, P2<0.001*, P3<0.001*, P4=0.004* P5<0.001* P6<0.001***
At the end cycle	7.55 ± 1.33	4.94 ± 0.92	4.33 ± 1.02	3.52 ± 0.85	**<0.001***	**P1<0.001*, p2<0.001*, P3<0.001*, P4=0.031*, P5<0.001*, P6=0.004***
Serum soluble FasL (ng/mL						
At baseline	7.43 ± 0.86	7.46 ± 1.02	7.52 ± 0.91	7.86 ± 0.81	0.311	
After the 1st cycle	13.66± 2.39	10.24 ± 1.04	8.83 ± 0.93	8.96 ± 0.88	**<0.001***	**P1<0.001*, p2<0.001*, p3<0.001*, p4<0.001* P5<0.001*** P6=0.618
At the end cycle	19.62± 2.48	10.59 ± 1.28	9.18 ± 1.07	8.84 ± 0.86	**<0.001***	**P1<0.001*, p2<0.001*, p3<0.001*, p4<0.001* P5<0.001*** P6=0.222
MDA (nmol/ mL)						
At baseline	11.91 ± 2.45	11.96± 2.91	12.07±2.7	12.87 ± 2.63	0.546	
After the 1st cycle	59.51 ± 13.5	27.28 ± 4.53	26.71 ± 5.15	26.83 ± 3.97	**<0.001***	**P1<0.001*, P2<0.001*, P3<0.001*,** P4=0.681 P5=0.714 P6=0.924
At the end cycle	126.23± 10.79	36.68 ± 6.18	32.55 ± 5.11	29.59 ± 5.59	**<0.001***	**P1<0.001*, P2<0.001*, P3<0.001*, P4=0.013***

						P5<0.001* P6=0.057

Data presents as mean ± SD. MDA: malondialdehyde. *: significant as P value ≤ 0.05, P1: P value between group I & II, P2: P value between group I and III, P3: P value between group I & IV, P4: P value between group II & III, P5: P value between group II & IV, P6: P value between group III & IIV.

The OS probability at 24 months for the whole studied sample was 67% (95% CI: 58 to 78%). The results revealed the presence of significant differences among the treatment groups (p = 0.036), as all the Mg treatment groups had a significantly better OS than control group, while the differences between the Mg groups were non-significant. This finding was also supported by the analysis comparing Mg intake to the control group, as OS probability at 24 months was 76% (95% CI: 67 to 88%) in patients treated with Mg compared to 38% only (95% CI: 21 to 68%) in the control group (p = 0.004). Previous smoking and lower survival probability at 24 months had significant correlation compared to patients who never smoked (OS [95% CI]: 43 [25 to 74] versus 74 [64 to 86], p = 0.002). The analysis revealed a lack of significant differences regarding the OS analysis according to age, sex, ECOG performance status, family history, and the tumor's anatomical site (all p-values >0.05).

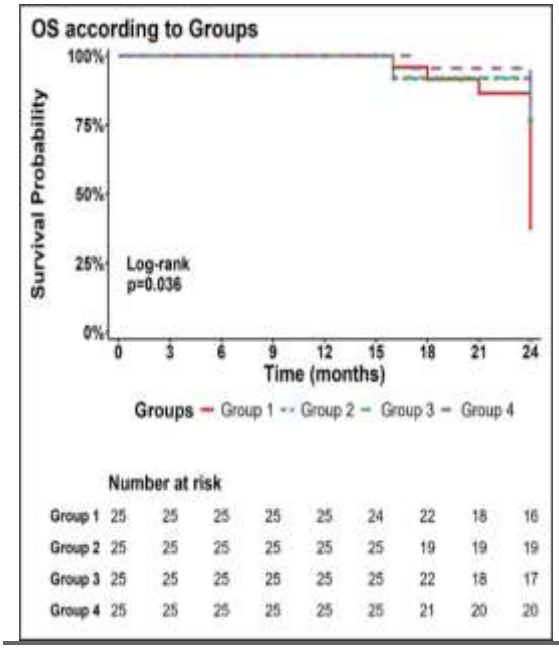
Univariable Cox proportional hazards regression was conducted to assess factors contributing to overall survival. The results showed a better prognosis with Mg intake (HR: 0.316; 95% CI: 0.147 to 0.679, p = 0.003), while previous smoking was associated with an inferior OS (HR: 3.181; 95% CI: 1.463 to 6.917; p = 0.003). The univariable Cox regression analysis did not reveal any significant correlation between overall survival and any of the other factors. **Table 4, Figure 1**

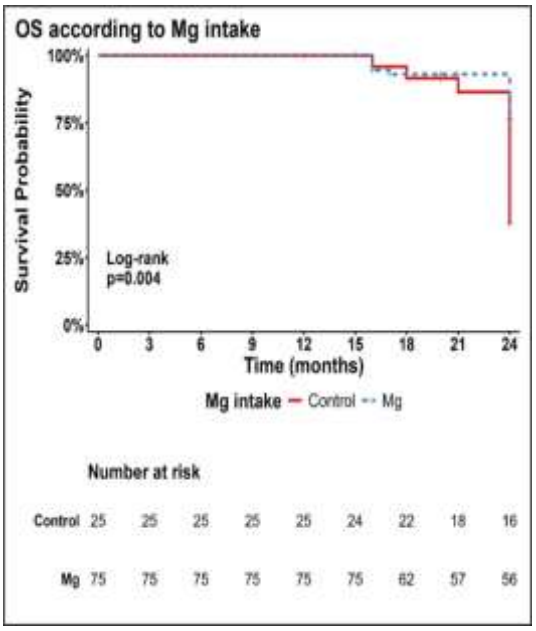
Table 4: Univariable analysis of overall survival according to patients' characteristics

Characteristic	**OS % (95% CI)**	**Log rank test**	**Univariable Cox PH regression**	
	At 24 Months	**p-value** a	**Unadjusted HR (95% CI)**	**p-value** a
Overall	67 (58 to 78)	–	–	–
Groups	–	**0.036***	–	–
Control	38 (21 to 68)	**Pairwise comparisons:** Control vs. Mg 1g = 0.026* Control vs. Mg 2g = 0.038* Control vs. Mg 3g = 0.017* Mg 1g vs. Mg 2g = 0.933 Mg 1g vs. Mg 3g = 0.951 Mg 2g vs. Mg 3g = 0.876	–	–
Mg 1g	77 (61 to 97)		0.311 (0.109 to 0.888)	**0.029***
Mg 2g	76 (59 to 97)		0.336 (0.118 to 0.955)	**0.041***
Mg 3g	76 (60 to 97)		0.303 (0.106 to 0.864)	**0.026***
Mg intake	–	**0.004***	–	–
Control	38 (21 to 68)	–	–	
Mg	76 (67 to 88)	–	0.316 (0.147 to 0.679)	**0.003***
Age group	–	0.795		
> 60 years	61 (42 to 88)	–	–	
≤60 years	69 (58 to 81)	–	0.865 (0.366 to 2.048)	0.742
Sex	–	0.122	–	–
Male	–	–	–	–
Female	58 (43 to 79)	–	1.770 (0.831 to 3.766)	0.139
Previous smoking	–	**0.002***	–	–
No	74 (64 to 86)	–	–	–
Yes	43 (25 to 74)	–	3.181 (1.463 to 6.917)	**0.003***

Characteristic	OS % (95% CI)	Log rank test	Univariable Cox PH regression	
	At 24 Months	p-value a	Unadjusted HR (95% CI)	p-value a
ECOG performance status	–	0.458	–	–
0	64 (51 to 79)	–	–	–
1	72 (59 to 88)	–	0.741 (0.339 to 1.620)	0.453
Family history	–	0.815	–	–
Negative	68 (58 to 79)	–	–	–
Positive	63 (38 to 100)	–	1.144 (0.344 to 3.799)	0.826
Anatomical site	–	0.915	–	–
Nasopharynx	65 (46 to 92)	–	–	–
Larynx	72 (55 to 94)	–	0.829 (0.267 to 2.570)	0.745
Oral cavity	71 (53 to 94)	–	0.879 (0.283 to 2.727)	0.824
Paranasal sinuses	71 (45 to 100)	–	0.875 (0.177 to 4.338)	0.870
Hypopharynx	57 (37 to 87)	–	1.358 (0.456 to 4.042)	0.582
Site	—	0.764	–	–
Non-oral	66 (55 to 79)	–	–	–
Oral cavity	71 (53 to 94)	–	0.866 (0.349 to 2.146)	0.756

Data presents as mean ± SD. Abbreviations: CI = Confidence Interval; HR = Hazard Ratio; PH: Proportional hazards a*p<0.05.





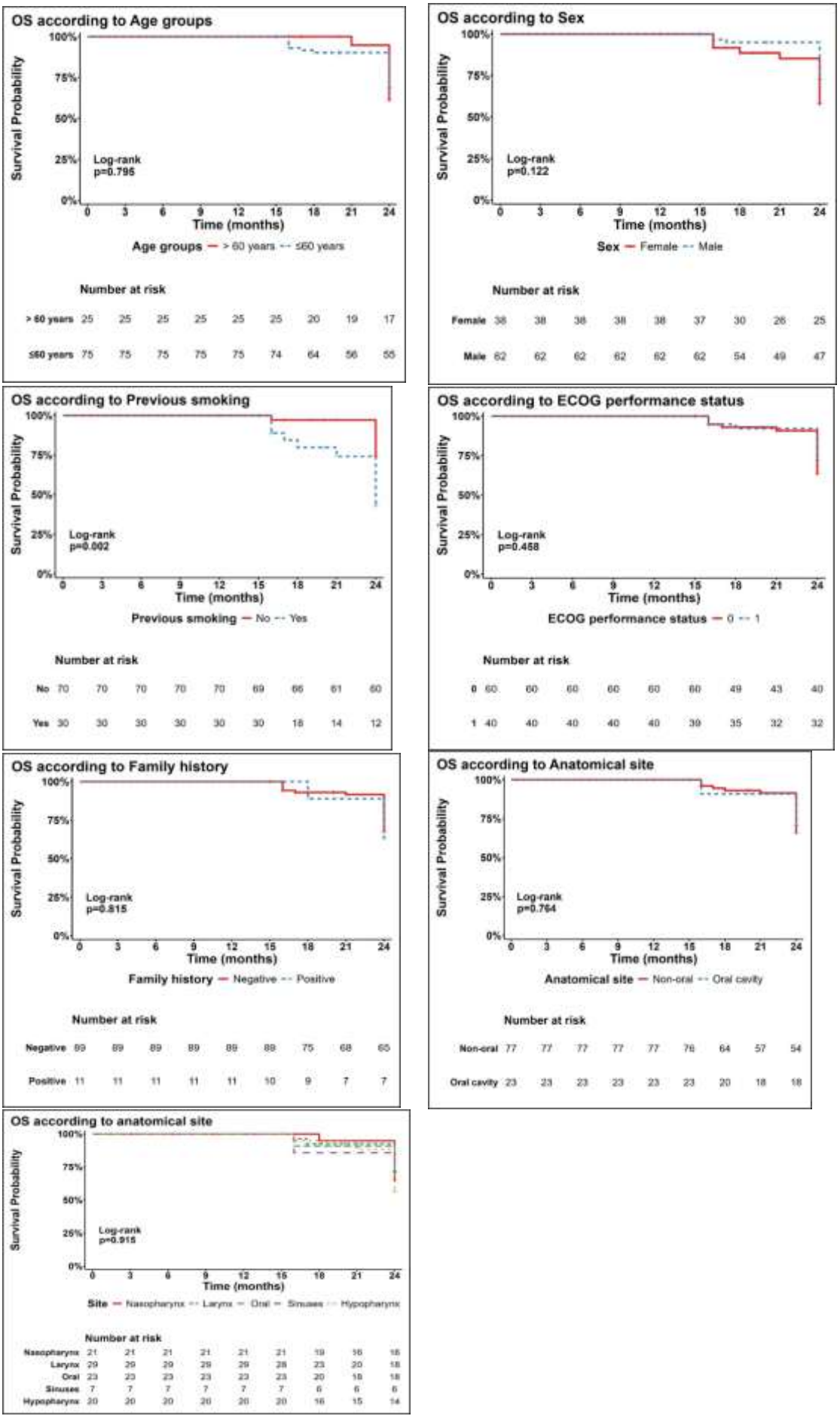


Figure 2: Kaplan-Meier curve for overall survival (OS) according to the treatment groups, Mg intake, age groups, sex, previous smoking, ECOG performance status, family history, tumor site (oral versus non-oral) and anatomical site of the tumor

Multivariable Cox proportional hazards regression was conducted for variables that showed a significant association in univariable regression. Mg intake still showed better overall survival compared to the control group after adjusting for the effect of previous smoking, where the adjusted HR was 0.361 (95% CI: 0.166 to 0.785; p = 0.010. The risk was still significantly higher among previous smokers compared to non-smokers, even after adjusting for the treatment effect (HR: 2.759; 95% CI: 1.254 to 6.070; p = 0.012). **Table 5**

Table 5: Multivariable Cox proportional hazards regression for overall survival

Characteristic		**Multivariable Cox PH regression**	
		Adjusted HR (95% CI)	**p-value** a
Mg intake	**Control**	—	
	Mg	0.361 (0.166 to 0.785)	**0.010***
Previous smoking		2.759 (1.254 to 6.070)	**0.012***

Abbreviations: CI = Confidence Interval; HR = Hazard Ratio; PH: Proportional hazard, a *p<0.05

DISCUSSION

HNC are a collection of malignancies that develop in the SC that line the mucosal surfaces of the oral cavity, larynx and pharynx. Early detection of cancer considerably enhances the prognosis, as treatment options as surgery, chemotherapy and radiation are customized to the cancer's stage and location [5]. Cisplatin remains a cornerstone chemotherapeutic agent for treating HNC. However, its medical value is frequently compromised by nephrotoxicity, a dose-dependent adverse effect that is the consequence of renal tubular cell injury. Cisplatin-induced AKI incidence is inconsistent, with studies reporting rates that range from 1% to 46%. This variability is influenced by patient-specific factors and dosing regimens [18].
Prophylactic Mg supplementation has emerged as a potential strategy to mitigate cisplatin-induced nephrotoxicity. Mg is thought to protect renal tubular cells by stabilizing cell membranes and reducing oxidative stress. It is suggested that intravenous Mg administration before cisplatin therapy may lower the risk of AKI, although standardized protocols regarding dosage and timing are yet to be established [19].
The baseline characteristics, including age, sex, weight, height, BMI, BSA, residence, and ECOG performance status, previous smoking and family history and regarding the anatomical site of HNC, the cisplatin dose/cycle, total Cisplatin dose and the total fluid volume were indifferent.
Suppadungsuk et al., [13] randomized controlled trial found that survival rate and overall cisplatin tumor response rate were consistent between the two groups, as were baseline characteristics. Regarding Kidney function tests, sCr at the end cycle was significantly lower in group 3 (Mg 16 Meq) and group 4 (Mg 24 Meq) compared to group 1 (control group).
In the same line with us, Danwilai et al., [20] in their meta-analysis illustrated Mg supplemented group had significantly reduced sCr changes and clearance than those in the controls at all cycles. They indicated that occurrence of severe cisplatin - induced nephrotoxicity in the first cycle and all other cycles of cisplatin-based chemotherapy reduced by Mg supplementation. And concluded that Mg supplementation has an inhibitory impact against cisplatin-induced nephrotoxicity, particularly severe nephrotoxicity. Mg supplementation may be evaluated by oncologists for patients who are receiving cisplatin treatment. Also, Saito et al., [21] investigated premedication with intravenous magnesium value in CIN prevention and relationship between its nephroprotective effect and serum Mg levels. Variation in sCr clearance found significantly reduced in the non-Mg group than Mg premedication group from start.
Platinum-containing medications (cisplatin, carboplatin, and oxaliplatin) have been utilized for the treatment of different solid cancers, including cervical cancer, lung cancer, HNC for a long time. This has resulted in hypomagnesemia that is secondary to chemotherapy. Hypomagnesemia is the most prevalent side effect of cisplatin, which results in a dose-dependent condition that impacts up to 90% of patients in the absence of preventive measures. Concurrent administration of histamine H2 antagonists or proton pump inhibitors (PPIs) has been recently implicated in the enhancement of the severity and frequency of cetuximab and panitumumab-induced hypomagnesemia. The onset of hypomagnesemia induced by anti-EGFR monoclonal antibodies is further affected by combined platinum treatment and prolonged exposure [22].
Various 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/m^2). Specifically examining Mg supplementation, studies 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 [23].

On contrary, Suppadungsuk et al., [13] aimed to determine whether preloading with Mg can prevent nephrotoxicity with a low-dose weekly cisplatin regimen and found that control group had a lower SCr. BUN was insignificantly different among groups at baseline, initial cycle and final cycle. eGFR at the end cycle was significantly higher in group 3 (Mg 16 Meq) and group 4 (Mg 24 Meq) compared to group 1 (control group).

Similarly, Saito et al., [21] validated our data and demonstrated that CIN did not occur in any patients who received Mg premedication. However, it did occur in 5 of 29 patients during the first cycle and in 6 patients during all subsequent cycles in patients who did not receive Mg premedication. The univariate analysis indicated that Mg premedication significantly decreased CIN.

Effect on renal function was in agreement with Crona et al., [24] indicated that Mg intake was nephron-protective, and enforced diuresis was useful for certain patients taking cisplatin. Regarding kidney injury biomarkers, Urine NGAL/CR after the initial cycle and final cycle was significantly lower in group 2 (Mg 8 Meq), group 3 (Mg 16 Meq) and group 4 (Mg 24 Meq) compared to group 1 (control group), was significantly lower in group 3 (Mg 16 Meq) and group 4 (Mg 24 Meq) compared to group 2 (Mg 8 Meq) and was significantly lower in group 4 (Mg 24 Meq) than group 3 (Mg 16 Meq). Urine KIM /Cr after the initial cycle and final cycle was significantly lower in group 2 (Mg 8 Meq), group 3 (Mg 16 Meq) and group 4 (Mg 24 Meq) compared to group 1 (control group), was significantly lower in group 3 (Mg 16 Meq) and group 4 (Mg 24 Meq) compared to group 2 (Mg 8 Meq) and was significantly lower in group 4 (Mg 24 Meq) than group 3 (Mg 16 Meq).

Similarly, Peres et al., [25] study noted that there was increased urine NGAL after each cycle of cisplatin. In contrast to non- AKI patients, the presence of AKI was associated with a rise in sCr, NGAL, C-reactive protein, and a decrease in GFR. NGAL levels increased in comparison to levels prior to cisplatin.

The current findings also were supported by Shinke et al., [26] who concluded that in lung cancer patients, urinary KIM-1 and MCP-1 may serve as biomarkers of cisplatin-induced AKI, either individually or in combination.

In alignment with previous data reading NGAL and KIM-1 a previous study by Latoch et al., [27] shown that a moderate correlation was found between NGAL/cr. and cisplatin cumulative dose. The NGAL/cr. ratio was only influenced by the cumulative dose of cisplatin as an independent factor in the multivariable model. Results indicated that urine KIM-1 and NGAL levels had increased for many years following solid tumors therapy at childhood. This increase was positively correlated with cisplatin cumulative dose.

Serum-soluble FasL after initial cycle and final cycle was significantly lower in group 2 (Mg 8 Meq), group 3 (Mg 16 Meq) and group 4 (Mg 24 Meq) compared to group 1 (control group), was significantly lower in group 3 (Mg 16 Meq) and group 4 (Mg 24 Meq) compared to group 2 (Mg 8 Meq). MDA after the 1st cycle was significantly lower in group 2 (Mg 8 Meq), group 3 (Mg 16 Meq) and group 4 (Mg 24 Meq) compared to group 1 (control group). MDA at the end cycle was significantly lower in group 2 (Mg 8 Meq), group 3 (Mg 16 Meq) and group 4 (Mg 24 Meq) compared to group 1 (control group), was significantly lower in group 3 (Mg 16 Meq) and group 4 (Mg 24 Meq) compared to group 2 (Mg 8 Meq).

In agreement with our findings, Kidera et al., [28] found IV Mg intake reduced risk, but our results did not show significant difference. Controls results in our study were explained by Holditch et al., [29] who found that molecular pathophysiology of cisplatin-induced AKI is of paramount importance in the establishment of effective tumor interventions with reduced nephrotoxicity.

Kumar et al., [30] observed that the cytotoxicity induced by cisplatin was increased when Mg deficiency or uptake inhibition found, whereas Mg supplementation provided protection against cytotoxicity. However, the in vitro destruction of CT26 tumor cells by cisplatin was not impeded by Mg deficiency or inhibition of Mg uptake.

The serum concentrations of magnesium may be significantly impacted by the sequential and/or concurrent use of drug combinations such as cetuximab and cisplatin. Hypomagnesemia was observed in up to 90% of patients who were administered cisplatin [31]. In 5% of individuals with HNC, treatment with cetuximab led to grade 3/4 hypomagnesaemia [32]. Nausea, vomiting, appetite loss and fatigue are the initial symptoms of hypomagnesemia. Conversely, neuromuscular excitability (tremor, muscle contractions, tingling, cramps, and seizures), cardiac effects (hypertension, prolonged QT interval, cardiomyopathy, life-threatening cardiac arrhythmias), and behavioral changes (depression, confusion, psychosis) are the symptoms of severe Mg deficiency [22]. Additionally, the modulation of calcium and potassium is closely linked to the concentration of magnesium in the serum. Therefore, cisplatin can also

result in hypocalcemia, hypokalemia, hypophosphatemia, and hyponatremia, in addition to hypomagnesemia [33].

In the current study, the OS probability at 24 months for the whole studied sample was 67% (95% CI: 58 to 78%). The results revealed the presence of significant differences among the treatment groups (p = 0.036), as all the Mg treatment groups had a significantly better OS than group 1 and differences of Mg groups was insignificant. Univariable Cox proportional hazards regression showed a better prognosis with Mg intake (HR: 0.316; 95% CI: 0.147 to 0.679, p = 0.003). Multivariable Cox proportional hazards regression revealed that Mg intake still showed better overall survival compared to the control group after adjusting for the effect of previous smoking, where the adjusted HR was 0.361 (95% CI: 0.166 to 0.785; p = 0.010.

In agreement with the current findings, Liu et al., [16] revealed correlation between hypomagnesemia and survival in patients with HNC who received concurrent chemoradiation with weekly infusions of cisplatin and/or carboplatin. They concluded that hypomagnesemia occurrence was a significant predictor of a shorter OS in patients with HNC and managed by chemoradiation with carboplatin or cisplatin. A reduced survival was discovered to be associated with more severe hypomagnesemia. Improving their approach to the prevention, detection, and treatment of hypomagnesemia is essential. Clinical outcomes may be enhanced by the prevention and hypomagnesemia mitigation, which may be an essential component of platinum-based regimens.

The study limitations were that we included small sample size from only one center and lack of assessing more parameters such as such as potential risk factors for cisplatin-induced nephrotoxicity.

CONCLUSIONS

From our study results, Mg can be used as a protective agent in cisplatin induced nephrotoxicity as it decreases sCr, BUN, and increase eGFR compared to cisplatin alone regimen. It also lowers kidney injury biomarkers including Urine KIM-1/Cr and urine NGAL, sFasL, urinary Malondialdehyde in regimen including Mg at different doses compared to cisplatin alone regimen.

Therefore, in cases of cisplatin-induced nephrotoxicity, we suggest magnesium use as a protective agent and we recommend utilizing the same study methodology on further studies larger sample size and multiple centers.

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REFERENCES:

1. Daraei P, Moore CE. Racial Disparity Among the Head and Neck Cancer Population. J Cancer Educ. 2015;30:546-51.
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136:359-86.
3. Jou A, Hess J. Epidemiology and Molecular Biology of Head and Neck Cancer. Oncol Res Treat. 2017;40:328-32.
4. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, Curado MP, Ferlay J, Franceschi S, et al. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. J Clin Oncol. 2013;31:50-69.
5. Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. Nat Rev Dis Primers. 2020;6:92-113.
6. Imbesi Bellantoni M, Picciolo G, Pirrotta I, Irrera N, Vaccaro M, Vaccaro F, et al. Oral Cavity Squamous Cell Carcinoma: An Update of the Pharmacological Treatment. Biomedicines. 2023;11:34-76.
7. Shin KH, Lee KR, Kang MJ, Chae YJ. Strong inhibition of organic cation transporter 2 by flavonoids and attenuation effects on cisplatin-induced cytotoxicity. Chem Biol Interact. 2023;379:11-20.
8. Fang CY, Lou DY, Zhou LQ, Wang JC, Yang B, He QJ, et al. Natural products: potential treatments for cisplatin-induced nephrotoxicity. Acta Pharmacol Sin. 2021;42:1951-69.
9. Noce A, Marrone G, Di Lauro M, Mitterhofer AP, Ceravolo MJ, Di Daniele N, et al. The Onco-Nephrology Field: The Role of Personalized Chemotherapy to Prevent Kidney Damage. Cancers (Basel). 2023;15:34-76.
10. Santos MLC, de Brito BB, da Silva FAF, Botelho A, de Melo FF. Nephrotoxicity in cancer treatment: An overview. World J Clin Oncol. 2020;11:190-204.
11. Workeneh BT, Uppal NN, Jhaveri KD, Rondon-Berrios H. Hypomagnesemia in the Cancer Patient. Kidney360. 2021;2:154-66.
12. Liu W, Qdaisat A, Soliman PT, Ramondetta L, Lopez G, Narayanan S, et al. Hypomagnesemia and Survival in Patients with Ovarian Cancer Who Received Chemotherapy with Carboplatin. Oncologist. 2019;24:312-7.
13. Suppadungsuk S, Phitakwatchara W, Reungwetwattana T, Pathumarak A, Phakdeekitcharoen B, Kitiyakara C, et al. Preloading magnesium attenuates cisplatin-associated nephrotoxicity: pilot randomized controlled trial (PRAGMATIC study). ESMO Open. 2022;7:10-35.
14. Yoshida T, Niho S, Toda M, Goto K, Yoh K, Umemura S, et al. Protective effect of magnesium preloading on cisplatin-induced nephrotoxicity: a retrospective study. Jpn J Clin Oncol. 2014;44:346-54.

15. Yamamoto Y, Watanabe K, Tsukiyama I, Matsushita H, Yabushita H, Matsuura K, et al. Nephroprotective effects of hydration with magnesium in patients with cervical cancer receiving cisplatin. Anticancer Res. 2015;35:200-4.
16. Liu W, Qdaisat A, Ferrarotto R, Fuller CD, Guo M, Meyer LA, et al. Hypomagnesemia and survival in patients with head and neck cancers who received primary concurrent chemoradiation. Cancer. 2021;127:528-34.
17. López-Jornet P, Camacho-Alonso F, López-Tortosa J, Tovar TP, Rodríguez-Gonzales MA. Assessing quality of life in patients with head and neck cancer in Spain by means of EORTC QLQ-C30 and QLQ-H&N35. J Craniomaxillofac Surg. 2012;40:614-20.
18. Ranasinghe R, Mathai ML, Zulli A. Cisplatin for cancer therapy and overcoming chemoresistance. Heliyon. 2022;8:66-78.
19. Gupta S, Glezerman IG, Hirsch JS, Chewcharat A, Wells SL, Ortega JL, et al. Intravenous Magnesium and Cisplatin-Associated Acute Kidney Injury. JAMA Oncol. 2025;11:636-43.
20. Danwilai K, Lohitnavy O, Sakunrag I, Dilokthornsakul P. The effect of magnesium supplementation on cisplatin induced nephrotoxicity: A systematic review and meta-analysis. Pharm Sci Asia. 2021;48:43-65.
21. Saito Y, Kobayashi M, Yamada T, Kasashi K, Honma R, Takeuchi S, et al. Premedication with intravenous magnesium has a protective effect against cisplatin-induced nephrotoxicity. Support Care Cancer. 2017;25:481-7.
22. Liamis G, Hoorn EJ, Florentin M, Milionis H. An overview of diagnosis and management of drug-induced hypomagnesemia. Pharmacol Res Perspect. 2021;9:82-99.
23. Ilhan Y, Onder A, Ozbay M, Karakaya G, Goksu SS, Ozturk B, et al. Protective effect of magnesium preloading on cisplatin-induced nephrotoxicity: which dose is more suitable? Eur Rev Med Pharmacol Sci. 2024;28:36-78.
24. Crona DJ, Faso A, Nishijima TF, McGraw KA, Galsky MD, Milowsky MI. A Systematic Review of Strategies to Prevent Cisplatin-Induced Nephrotoxicity. Oncologist. 2017;22:609-19.
25. Peres LA, da Cunha AD, Jr., Assumpção RA, Schäfer A, Jr., da Silva AL, Gaspar AD, et al. Evaluation of the cisplatin nephrotoxicity using the urinary neutrophil gelatinase-associated lipocalin (NGAL) in patients with head and neck cancer. J Bras Nefrol. 2014;36:280-8.
26. Shinke H, Masuda S, Togashi Y, Ikemi Y, Ozawa A, Sato T, et al. Urinary kidney injury molecule-1 and monocyte chemotactic protein-1 are noninvasive biomarkers of cisplatin-induced nephrotoxicity in lung cancer patients. Cancer Chemother Pharmacol. 2015;76:89-96.
27. Latoch E, Konończuk K, Muszyńska-Rosłan K, Taranta-Janusz K, Wasilewska A, Szymczak E, et al. Urine NGAL and KIM-1-Tubular Injury Biomarkers in Long-Term Survivors of Childhood Solid Tumors: A Cross-Sectional Study. J Clin Med. 2021;10:34-67.
28. Kidera Y, Kawakami H, Sakiyama T, Okamoto K, Tanaka K, Takeda M, et al. Risk factors for cisplatin-induced nephrotoxicity and potential of magnesium supplementation for renal protection. PLoS One. 2014;9:10-9.
29. Holditch SJ, Brown CN, Lombardi AM, Nguyen KN, Edelstein CL. Recent Advances in Models, Mechanisms, Biomarkers, and Interventions in Cisplatin-Induced Acute Kidney Injury. Int J Mol Sci. 2019;20:87-112.
30. Kumar G, Solanki MH, Xue X, Mintz R, Madankumar S, Chatterjee PK, et al. Magnesium improves cisplatin-mediated tumor killing while protecting against cisplatin-induced nephrotoxicity. Am J Physiol Renal Physiol. 2017;313:339-50.
31. Oronsky B, Caroen S, Oronsky A, Dobalian VE, Oronsky N, Lybeck M, et al. Electrolyte disorders with platinum-based chemotherapy: mechanisms, manifestations and management. Cancer Chemother Pharmacol. 2017;80:895-907.
32. Abu-Amna M, Bar-Sela G. Increase in cetuximab-induced skin rash and hypomagnesemia in patients receiving concomitant treatment with proton pump inhibitors (PPIs): a possible drug interaction? Cancer Chemother Pharmacol. 2019;83:545-50.
33. Alrfaei BM, Almutairi AO, Aljohani AA, Alammar H, Asiri A, Bokhari Y, et al. Electrolytes Play a Role in Detecting Cisplatin-Induced Kidney Complications and May Even Prevent Them-Retrospective Analysis. Medicina (Kaunas). 2023;59:65-94.

AKI	Acute kidney injury
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
BSA	Body surface area
BUN	Blood urea nitrogen
ECOG	Eastern cooperative oncology group performance status
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
HNC	Head and neck cancers
MDA	Malondialdehyde
Mg	Magnesium
NGAL	Neutrophil gelatinase associated lipocalin
OCT2	Organic cation transporter 2
sCr	Serum creatinine
sFasL	Serum soluble Fas ligand