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Review

The effect of magnesium supplementation on cisplatin induced nephrotoxicity: A systematic review and meta-analysis

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ABSTRACT

Nephrotoxicity is a serious side effect of cisplatin. Magnesium supplement can reduce this side effect, although previous studies demonstrated the effect on cisplatin - induced nephrotoxicity (CIN), with some showing no effect. This study aimed to summarize the effect of magnesium supplement on CIN. We systematically searched PubMed, Cochrane Library, Web of Science, Scopus, EMBASE and www.clinicaltrial.gov for all relevant studies. All clinical studies comparing the risk of CIN in patients who received magnesium supplement and the control groups were included. Our primary outcome examined the occurrence of severe nephrotoxicity. The secondary outcome was the occurrence of all grades of nephrotoxicity and changes in serum creatinine (SCr) and creatinine clearance (CrCl). Random-effects model was used to determine pooled effect size for nephrotoxicity-related outcomes. A total of 4,053 studies were retrieved but only 12 studies were included. Nine studies were retrospective observational studies, while two studies were randomized controlled trials and one study was prospective study. All studies were conducted with patients that had solid tumors and receiving cisplatin >50 mg/m^2/cycle.Meta-analysis indicated that magnesium supplementation could reduce the occurrence of severe CIN in the first cycle and all other cycles of cisplatin-based chemotherapy (RR 0.19, 95%CI; 0.11 - 0.33 and RR 0.28, 95%CI; 0.19 - 0.43, respectively). Similarly, changes in SCr and CrCl in the magnesium-supplemented group were significantly lower than those in the control group for both the first cycle and all other cycles ($p<0.001$). With the current evidence, magnesium supplementation possesses a protective effect for CIN, especially for severe nephrotoxicity. Oncologists may well consider supplementing magnesium for patients who are treated with cisplatin.

1. INTRODUCTION

Cisplatin has a well-established role in the treatment of many cancers, however, cisplatin-induced nephrotoxicity (CIN) is a common adverse effect and frequently limits its use in practice. Since cisplatin is predominantly excreted in the kidneys, the accumulation of the cisplatin in the renal tubular cells directly causes a damage to renal tubules. This results in decreased glomerular filtration rate and tubular reabsorption of electrolytes and leads to acute kidney injury and electrolyte wasting, specifically magnesium. Hence, magnesium supplementation is common practice

for prevention of hypomagnesemia which generally occur in about 10 days after cisplatin treatment[1-4]. Important risk factors of CIN are dose and frequency of cisplatin administration, history of cisplatin use, patients'age, performance status measured by Eastern Cooperative Oncology Group (ECOG) scale, use of nonselective nonsteroidal anti-inflammatory drugs, hypoalbuminemia and hydration without magnesium supplementation[5-8]. Intravenous hydration is the standard prevention of CIN but only hydration might not be sufficient to prevent CIN.

Magnesium supplementation is an option to prevent CIN. It has been known that cisplatin causes hypomagnesemia in approximately 90%of the patients and magnesium deficiency itself may potentiate CIN[9]. The occurrence of CIN depends on the number of cycles, which reflects the cumulative dose of cisplatin[10-13]. Some clinical studies have reported the advantage of magnesium supplementation in CIN prevention[8,14-24] but some clinical studies showed no protective effects[25-27]. To date, there is also no international guidelines which highly recommend magnesium supplement in patients receiving cisplatin due to the lack of evidence. The summary of evidence related to the effect of magnesium on CIN prevention is currently needed. Therefore, this systematic review and meta-analysis aimed to determine the clinical effect of magnesium supplementation on CIN prevention.

2. MATERIALS AND METHODS

This article was conducted according to the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement. All meta-analyses were performed by using results from previously published studies, and thus no ethical approval and informed consent are required.

2.1. Search strategy and selection criteria

PubMed, Cochrane Library, Web of Science, Scopus, EMBASE and www.clinicaltrial.gov were searched for relevant studies up to February 2018. Strategic search terms were cisplatin, platinum*, and magnesium. The eligibility criteria were as follows: 1) studies conducted in adult patients diagnosed with solid tumor or hematologic malignancy who received cisplatin - based chemotherapy, 2) studies comparing the effect of magnesium supplementation with controls, and 3) studies reporting nephrotoxicity-related outcomes. No language restriction was applied. Titles and abstracts were screened according to the eligibility criteria. Full-text articles of potential studies were retrieved and were subsequently assessed independently by KD and PD. Any disagreements were settled by discussion and consensus.

2.2. Data extraction and quality assessment

Data extraction was undertaken by KD using a standard data extraction form and then verified by PD. The extracted data included study characteristics (first author, publication year, journal, study objective, study design, setting, country, diagnosis, and sample size), patients'characteristics, characteristics of intervention and comparator, and outcomes. The pre-specified primary outcome was severe nephrotoxicity, defined as grade 2 or more according to Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v.4.0.)[28] Pre-specified secondary outcomes were the occurrence of any grades of nephrotoxicity and changes in SCr and CrCl. Quality of included studies were assessed using the Revised Cochrane risk of bias tool for randomized trials (RoB 2.0)[29] for randomized trials and Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I)[30] for non-randomized trial. The assessment was independently performed by KD and PD.

2.3. Statistical analysis

Meta-analyses were performed under the Der Simonian and Laird random-effects model[31]. The pooled relative risk with its corresponding 95% confidence interval (95%CI) was presented for the occurrence of nephrotoxicity, while the pooled mean difference (MD) with its corresponding 95%CI was presented for the changes in SCr and CrCl. Heterogeneity was assessed by the I^2-statistic. Threshold of I^2 were interpreted in accordance with the magnitude and direction of effects and strength of evidence of heterogeneity. I^2-values greater than 50% indicated substantial heterogeneity[32]. Data from included studies were pooled using STATA version 15 (STATA Corp, College Station, TX, USA).

3. RESULTS

After identified through database searching and duplicate removed. We found a total 4,053 studies but only twelve studies[8,17-27] were included in qualitative synthesis. Of those, ten studies provided sufficient data to perform

Table 1. Baseline characteristics of included studies.

Study ID	Country	Cancer type	Study design	Age; year (I/C)	Number of patients (I/C)	Chemotherapy regimen	Cisplatin dose	Interventions	Control	Reported outcomes
Kidera (2014)[8]	Japan	All type	Retrospective Study	NA	67/334	Various regimens	≥ 60 mg/m^2	20 mEq $MgSO_4$ IV plus hydration plus mannitol plus furosemide	Hydration plus mannitol plus furosemide	Grade nephrotoxicity* and ΔSCr
Willox JC (1986)[17]	UK	Testicular cancer	Randomized controlled trials	29/33	8/9	cisplatin, vinblastine, bleomycin	20 mg/m^2 day 1 – 5	8 mmol $MgSO_4$ IV day 1 to 5 plus hydration then magnesium citrate 10 mmol oral tid daily	Hydration	Urine NAG activity
Yamamoto Y (2016)[18]	Japan	Gynecological cancer	Retrospective Study	58/58	37/37	cisplatin plus irinotecan, or monthly paclitaxel or weekly paclitaxel, or monthly docetaxel, or weekly docetaxel, or doxorubicin, or etoposide	50 mg/m^2 except irinotecan plus cisplatin 60 mg/m^2	15 mEq $MgSO_4$ IV plus hydration day 1 then 5 mEq $MgSO_4$ IV day 2 and 3	Hydration	RIFLE criteria
Yoshida T (2014)[19]	Japan	Thoracic malignancy	Retrospective Study	64/65	161/335	cisplatin plus vinorelbine or pemetrexed or irinotecan or etoposide or gemcitabine or amurubicin or docetaxel	>60 mg/m^2	8 mEq $MgSO_4$ IV plus hydration plus mannitol	Hydration plus mannitol	Grade nephrotoxicity*
Hirai S (2013)[20]	Japan	Esophageal and hypopharyngeal cancer	Retrospective Study	64/66	10/13	cisplatin plus 5-fluorouracil	80 mg/m^2	20 mEq $MgSO_4$ IV plus hydration plus mannitol	Hydration plus mannitol	Grade nephrotoxicity*
Muraki K (2012)[21]	Japan	Lung cancer	Retrospective Study	63/60	20/30	cisplatin plus pemetrexed	80 mg/m^2	8 mEq $MgSO_4$ IV plus hydration plus mannitol plus furosemide	Hydration plus mannitol plus furosemide	ΔSCr, ΔCrCl#
Bodnar L (2008)[22]	Poland	Ovarian cancer	Randomized controlled trials	53/54	20/20	paclitaxel 135mg/m^2 IV over a 24-h on day 1 followed by 75mg/m^2 of IV infusion cisplatin on day 2	75 mg/m^2	5 g $MgSO_4$ IV plus prehydration then magnesium subcarbonate 500 mg oral tid	Placebo and hydration	ΔSCr, ΔCrCl#
Kimura T (2018)[23]	Japan	Head and neck cancer	Retrospective Study	62/62	56/65	cisplatin plus 5-fluorouracil	80 mg/m^2	20 mEq $MgSO_4$ IV plus hydration	Hydration	ΔCrCl#

Table 1. Baseline characteristics of included studies. (cont.)

Study ID	Country	Cancer type	Study design	Age; year (I/C)	Number of patients (I/C)	Chemotherapy regimen	Cisplatin dose	Interventions	Control	Reported outcomes
Konishi H (2018)[24]	Japan	Esophageal squamous cell carcinoma	Prospective cohort Study	67/65	37/18	cisplatin plus 5-fluorouracil, cisplatin, docetaxel, and 5-fluorouracil (DCF) regimen	≥ 60 mg/m^2	8 mEq $MgSO_4$ IV plus hydration plus mannitol plus furosemide	Hydration plus mannitol plus furosemide	Grade nephrotoxicity*
Oka T (2014)[25]	Japan	Lung cancer	Retrospective Study	65/66	44/41	cisplatin plus vinorelbine or pemetrexed or irinotecan or etoposide or S-1 or gemcitabine	80 mg/m^2	8 mEq $MgSO_4$ IV plus hydration plus mannitol plus furosemide	Hydration plus mannitol plus furosemide	Grade nephrotoxicity* and ΔSCr, ΔCrCl#
Saito Y (2017)[26]	Japan	head and neck cancer	Retrospective Study	63/58	29/29	cisplatin, docetaxel, and 5-fluorouracil (DCF) regimen	75 mg/m^2	20 mEq $MgSO_4$ IV plus hydration plus mannitol	Hydration plus mannitol	Grade nephrotoxicity* and ΔSCr, ΔCrCl#
Yamaguchi T (2017)[27]	Japan	Lung cancer	Retrospective Study	65/63	60/62	cisplatin plus vinorelbine or pemetrexed or pemetrexed+ bevacizumab or irinotecan or etoposide or gemcitabine or irinotecan	>50 mg/m^2	8 mEq $MgSO_4$ IV plus hydration plus furosemide	Hydration plus mannitol	Grade nephrotoxicity* and ΔSCr

UK: *United Kingdom,* I/C: intervention/control, NA: not available, $MgSO_4$: Magnesium sulphate, Grade nephrotoxicity according to Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE V.4), ΔSCr: change in serum creatinine from baseline, ΔCrCl: change in creatinine clearance from baseline

* Grade nephrotoxicity according to Common TerminologyCriteria for Adverse Events (CTCAE), version 4.0

\# Cockcroft-Gault equation

meta-analysis[8,19-27] because 2 studies[17-18] reported different nephrotoxic - related outcome from ten studies (Figure 1). Nine studies were retrospective observational studies[8,18-21,23,25-27], whereas two studies were randomized controlled trials (RCTs)[17,22] and one study was prospective observational study[24]. All included studies were conducted in patients with solid tumors and receiving ≥50 mg/m^2/cycle of cisplatin-based chemotherapy. Intravenous magnesium sulfate ($MgSO_4$) administration (8-20 milliequivalence; mEq) prior to chemotherapy initiation was used as intervention of interest for eleven included studies[17-27]. Only one study administered intravenous $MgSO_4$ after chemotherapy[8]. Two studies also added oral magnesium supplementation afterwards[17,22]. Four studies reported both grade of nephrotoxicity and changes in SCr and/or CrCl[8,25-27], while three studies reported only grade of nephrotoxicity[19,20,24]. Three studies reported only changes in SCr or/and CrCl[21-23], and the other two studies reported other nephrotoxicity-related outcomes including urine N-acetyl- B-D-glucosaminidase (NAG) activity[17] and Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease (RIFLE) criteria[18]. The study characteristics of included studies were summarized in Table 1.

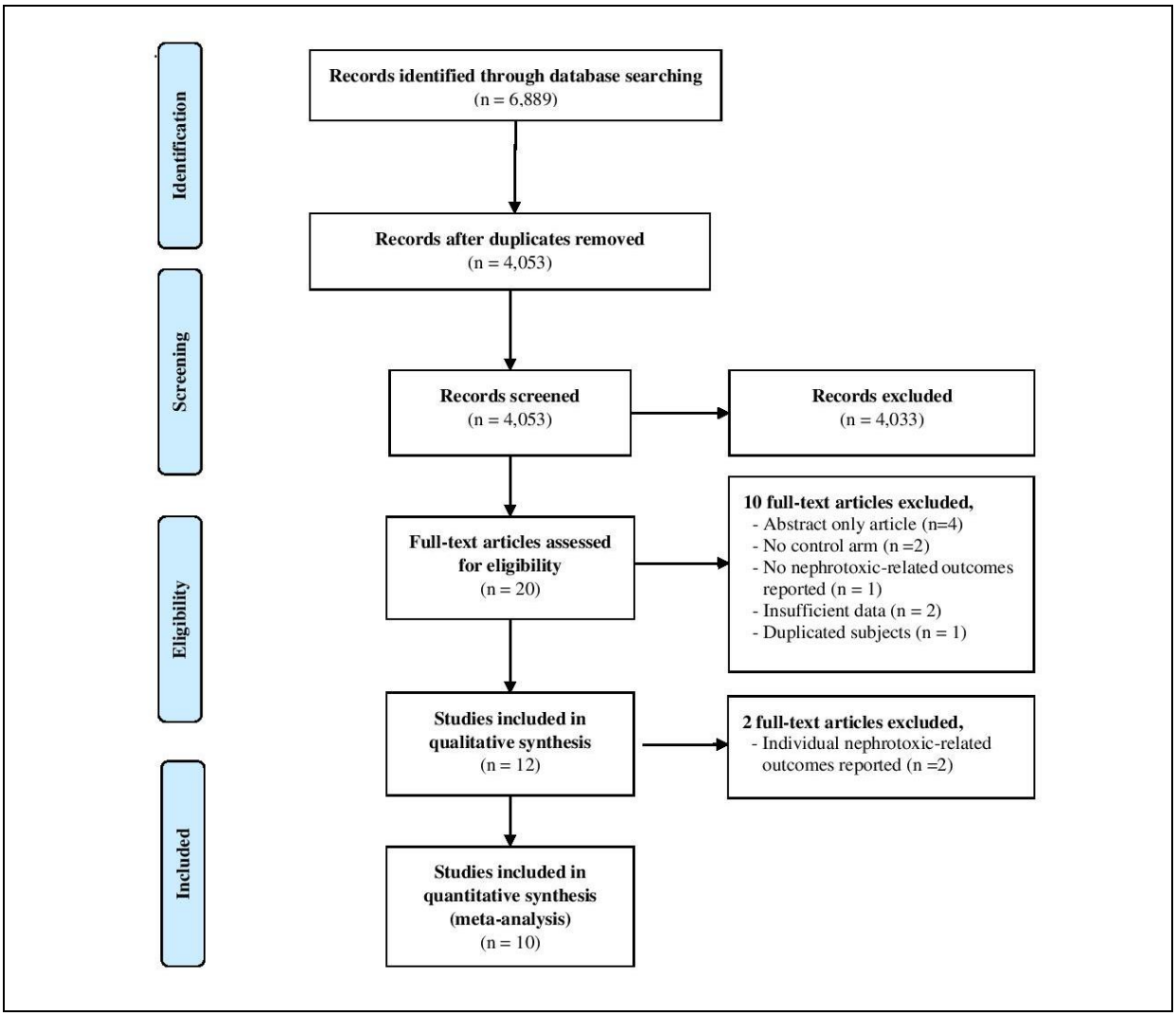

Figure 1. Flow diagram of literature retrieval and screening.

The quality of RCTs[17,22] studies demonstrated some concerns risk of bias due to insufficient information regarding the randomization process, i.e., there was no mention of method of random sequence generation and allocation concealment in the studies. In addition, a study by Willox JC et al did not report how the blinding process was performed[17]. The other ten observational studies[8,18-21,23-27] had serious risk of bias because of the lack of appropriate confounding adjustment and outcome measurement. The detailed quality assessment scores were reported in Table 2 and 3.

Table 2. Risk of bias assessment (Robin I).

Study ID	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Kidera	Serious	Low	Moderate	Low	Low	Serious	Moderate	Serious
Yamamoto Y	Serious	Low	Moderate	Low	Low	Serious	Moderate	Serious
Yoshida T	Serious	Low	Moderate	Low	Low	Serious	Moderate	Serious
Hirai S	Serious	Low	Moderate	Low	Low	Serious	Moderate	Serious
Muraki K	Serious	Low	Moderate	Low	Low	Serious	Moderate	Serious
Kimura T	Serious	Low	Moderate	Low	Low	Serious	Moderate	Serious
Konishi H	Serious	Low	Moderate	Low	Low	Serious	Moderate	Serious
Oka T	Serious	Low	Moderate	Low	Low	Serious	Moderate	Serious
Saito Y	Serious	Low	Moderate	Low	Low	Serious	Moderate	Serious
Yamaguchi T	Serious	Low	Moderate	Low	Low	Serious	Moderate	Serious

Table 3. Risk of bias assessment (ROB II).

Study ID	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall bias
Bodnar L	Some concerns	Low	Low	Low	Low	Some concerns
Willox JC	Some concerns	Some concerns	Low	Low	Low	Some concerns

Five studies[19-20,24,26-27] reported severe nephrotoxicity for all cycle. The meta-analysis showed that the occurrence of severe nephrotoxicity for all chemotherapy cycles was significantly lower in magnesium-supplemented group compared to control group (RR 0.28, 95%CI; 0.19 to 0.43; I^2=0%). The effect was likely to be dose - dependent. The RRs of magnesium-supplemented groups receiving 20 and 8 mEq of magnesium sulfate were 0.17 (95% CI 0.02 to 1.35; I^2=0%) and 0.29 (95% CI 0.19 to 0.45; I^2=0%), respectively (Figure 2).

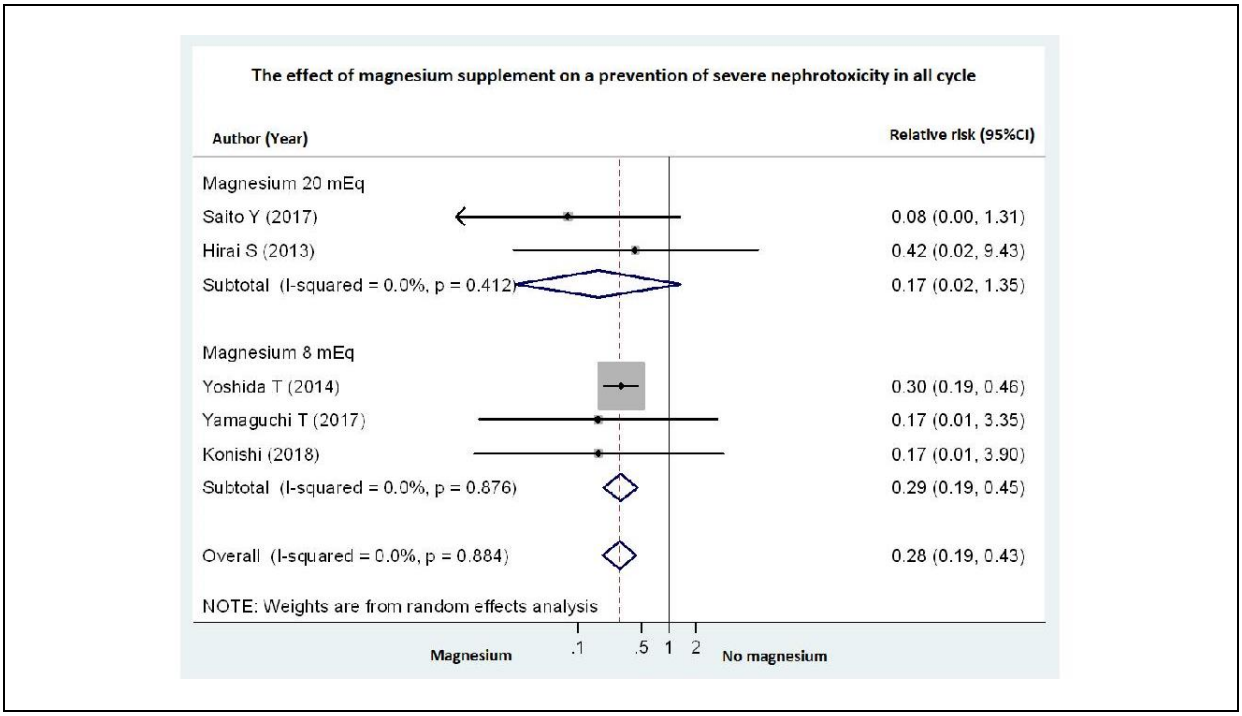

Figure 2. The effect of magnesium supplement on a prevention of severe nephrotoxicity* in all cycle.
Note: Severe nephrotoxicity was defined grade 2 or more of Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Table 4. The effect of magnesium supplementation on CIN.

Outcomes	Number of studies	Number of participants(I/C)	Number of events (I/C)	Relative risk (95%CI)	p-value	Heterogeneity (%I2)	Pooled studies
Severe nephrotoxicity (≥ Grade2 based on CTCAE version 4.0)							
All cycles of chemotherapy							
Any doses $MgSO_4$	5	297/457	22/344	0.28 (0.19 to 0.43)	<0.001	0.0%	Yoshida T (2014)[19], Hirai S (2013)[20], Konishi H (2018)[24], Saito Y (2017)[26], Yamaguchi T (2017)[27]
20 mEq $MgSO_4$	2	39/42	0/11	0.17 (0.02 to 1.35)	0.094	0.0%	Hirai S (2013)[20], Saito Y (2017)[26]
8 mEq $MgSO_4$	3	258/415	19/333	0.29 (0.19 to 0.45)	<0.001	0.0%	Yoshida T (2014)[19], Konishi H (2018)[24], Yamaguchi T (2017)[27]
First cycle of chemotherapy							
Any doses $MgSO_4$	5	294/467	9/90	0.19 (0.11 to 0.33)	<0.001	0.0%	Kidera (2014)[8],Yoshida T (2014)[19], Oka T (2014)[25], Saito Y (2017)[26], Yamaguchi T (2017)[27]
20 mEq $MgSO_4$	2	29/29	0/5	0.15 (0.06 to 0.38)	<0.001	0.0%	Kidera (2014)[8], Saito Y (2017)[26]
8 mEq $MgSO_4$	3	265/438	9/85	0.19 (0.08 to 0.47)	<0.001	16.9%	Yoshida T (2014)[19], Oka T (2014)[25], Yamaguchi T (2017)[27]
Any level of nephrotoxicity (All grades based on CTCAE version 4.0)							
All cycles of chemotherapy							
Any doses $MgSO_4$	5	297/457	116/344	0.44 (0.23 to 0.83)	0.011	55.7%	Yoshida T (2014)[19], Hirai S (2013)[20], Konishi H (2018)[24], Saito Y (2017)[26], Yamaguchi T (2017)[27]
20 mEq $MgSO_4$	2	39/42	0/11	0.10 (0.01 to 0.69)	0.020	0.0%	Hirai S (2013)[20], Saito Y (2017)[26]
8 mEq $MgSO_4$	2	258/415	116/333	0.55 (0.33 to 0.91)	0.019	51.2%	Yoshida T (2014)[19], Konishi H (2018)[24], Yamaguchi T (2017)[27]
First cycle of chemotherapy							
Any doses $MgSO_4$	5	361/801	135/463	0.42 (0.18 to 0.95)	0.036	97.6%	Kidera (2014)[8], Yoshida T (2014)[19], Oka T (2014)[25], Saito Y (2017)[26], Yamaguchi T (2017)[27]
20 mEq $MgSO_4$	2	96/363	4/128	0.15 (0.06 to 0.38)	<0.001	0.0%	Kidera (2014)[8], Saito Y (2017)[19]
8 mEq $MgSO_4$	3	265/438	131/335	0.63 (0.31 to 1.27)	0.197	97.6%	Yoshida T (2014)[19], Oka T (2014)[25], Yamaguchi T (2017)[27]

I/C: intervention/control, $MgSO_4$: Magnesium sulphate

The occurrence of severe nephrotoxicity for the first chemotherapy cycle of patients was also significantly lower in magnesium supplement group (RR 0.19, 95%CI 0.11 to 0.33; I^2=0%) and the nephroprotective effect was likely to be dose - dependent[8,19,25-27] (Figure 3). Similar to severe nephrotoxicity, the occurrence of all levels of nephrotoxicity was lower in magnesium-supplemented group. The RR of all levels of nephrotoxicity for all cycles was 0.44 (95%CI 0.23 to 0.83; I^2=55.7%), while that for the first cycle was 0.42 (95%CI 0.18 to 0.95; I^2=97.6%). The effect of magnesium supplement on a prevention of CIN both all cycle and the first cycle were presented in Table 4.

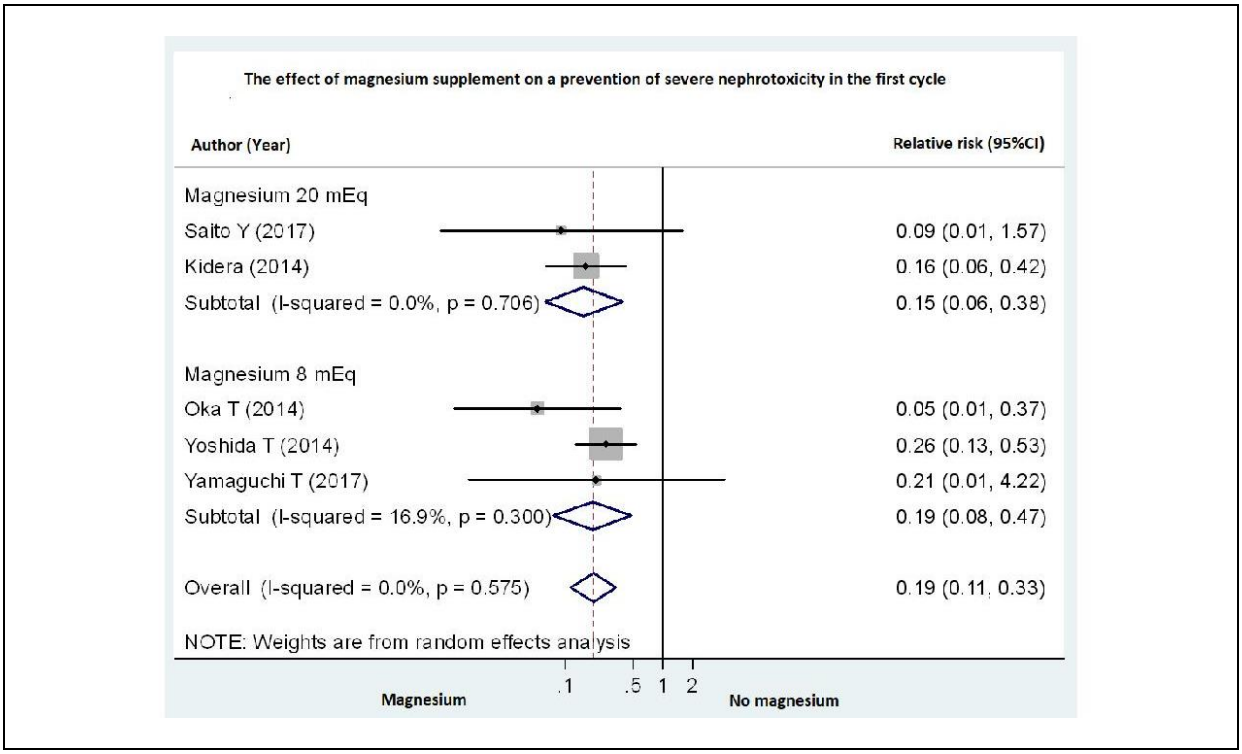

Figure 3. The effect of magnesium supplement on a prevention of severe nephrotoxicity* in first cycle.
Note: Severe nephrotoxicity was defined grade 2 or more of Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Seven studies provided data on changes in SCr and/or CrCl [8,21-23,25-27]. Our meta-analysis indicated that the increase in SCr in patients with magnesium supplementation was significantly lower than that in patients with control (MD = -0.2, 95%CI -0.27 to -0.13; I^2=60.1%) for all chemotherapy cycles. This result was in line with its protective effect on CIN. Similar to the analysis of all chemotherapy first cycles, the increase in SCr in patients with magnesium supplementation was also significantly lower than that in patients with control (MD =-0.19, 95% CI -0.25 to -0.12; I^2=88.6%]. Magnesium supplementation also significantly prevented the decrease in CrCl for all chemotherapy cycles and the first cycles. Mean differences of the decrease in CrCl for all cycles and for the first cycle were -11.33 (95% CI -14.15 to -8.51; I^2= 0.0%) and -12.02 (95% CI -14.83 to -9.22; I^2= 0.0%), respectively. The mean differences of both all cycle and the first cycle were presented in Table 5.

A study by Willox JC et al[17] reported the effect of magnesium supplementation on CIN by measuring urine NAG activity. Higher urine NAG activity indicated higher nephrotoxicity. The study reported that magnesium supplementation significantly reduced the urine NAG activity compared to control by the third cycle of chemotherapy (P<0.01). Another study by Yamamoto Y et al[18] reported the nephroprotective effect of 15 mEq magnesium supplementation on CIN using the RIFLE criteria. The study showed that the number of patients with moderate renal dysfunction, which was defined as an increase in SCr of ≥ 50% or a decrease in CrCl of ≤25% was significantly lower in patients with magnesium supplementation compared to controls (21.6% vs. 51.4%; P<0.01). However, the number of patients with severe renal dysfunction, which was defined as increase in SCr of ≥ 100% or a decrease in CrCl of ≤ 50%, was not statistically different (8.1% vs. 16.2%; P=0.29).

Table 5. The effect of magnesium supplementation on changes in SCr and CrCl.

Outcomes	Number of studies	Number of participants (I/C)	Mean difference (95%CI)	p-value	Heterogeneity ($\%I^2$)	Pooled studies
Increase of SCr						
All cycle						
Any doses $MgSO_4$	4	129/142	-0.20 (-0.27 to -0.13)	<0.001	60.1%	Muraki K (2012)[21], Bodnar L (2008)[22], Saito Y (2017)[26], Yamaguchi T (2017)[27]
≥20 mEq $MgSO_4$	2	49/50	-0.23 (-0.41 to -0.05)	0.011	81.4%	Bodnar L (2008)[22], Saito Y (2017)[26]
8 mEq $MgSO_4$	2	80/92	-0.18 (-0.24 to -0.12)	<0.001	20.4%	Muraki K (2012)[21], Yamaguchi T (2017)[27]
First cycle						
Any doses $MgSO_4$	5	220/487	-0.19 (-0.25 to -0.12)	<0.001	88.6%	Kidera (2014)[8], Bodnar L (2008)[22], Oka T (2014)[25], Saito Y (2017)[26], Yamaguchi T (2017)[27]
≥20 mEq $MgSO_4$	3	116/384	-0.21 (-0.31 to -0.11)	<0.001	81.5%	Kidera (2014)[8], Bodnar L (2008)[22], Saito Y (2017)[26]
8 mEq $MgSO_4$	2	104/103	-0.16 (-0.20 to -0.13)	<0.001	8.6%	Oka T (2014)[25], Yamaguchi T (2017)[27]
Decrease of CrCl						
All cycle						
Any doses $MgSO_4$	4	125/145	-11.33 (-14.15 to -8.51)	<0.001	0.0%	Muraki K (2012)[21], Bodnar L (2008)[22], Kimura T (2018)[23], Saito Y (2017)[26]
≥20 mEq $MgSO_4$	3	105/115	-11.87 (-16.65 to -7.08)	<0.001	29.3%	Bodnar L (2008)[22], Kimura T (2018)[23], Saito Y (2017)[26]
8 mEq $MgSO_4$	1	20/30	-11.42 (-16.13 to -6.72)	<0.001	NA	Muraki K (2012)[21]
First cycle						
Any doses $MgSO_4$	3	93/91	-12.02 (-14.83 to -9.22)	<0.001	0.0%	Bodnar L (2008)[22], Oka T (2014)[25], Saito Y (2017)[26]
≥20 mEq $MgSO_4$	2	49/50	-13.18 (-19.28 to -7.08)	<0.001	0.0%	Bodnar L (2008)[22], Saito Y (2017)[26]
8 mEq $MgSO_4$	1	44/41	-11.71 (-14.87 to -8.55)	<0.001	0.0%	Oka T (2014)[25]

I/C: intervention/control, ΔSCr: change in serum creatinine from baseline, ΔCrCl: change in creatinine clearance from baseline

4. DISCUSSION

Our systematic review and meta-analysis provided a most updated and comprehensive evidence of magnesium supplementation on prevention of CIN. We observed that a supplementation of 8 - 20 mEq magnesium of any cycle of cisplatin-based chemotherapy could reduce the risk of nephrotoxicity induced by cisplatin, especially for severe nephrotoxicity.

Cisplatin has been widely used for treatment of several types of solid tumors. However, nephrotoxicity is one of the major dose-limiting adverse effects. Cisplatin is excreted in the urine via glomerular filtration and tubular secretion. The secretion of cisplatin in the proximal tubules is mediated by various transporters. In humans, cisplatin enters the tubular cells from basolateral side via organic cation transporters 2 (OCT2), accumulates in these cells, and then transports into the urine at the apical side via multidrug and toxin extrusion (MATE) transporters. Some OCT2 inhibitors such as cimetidine and corticosterone have been demonstrated to decrease the cytotoxicity and renal toxicity induced by cisplatin[33]. Direct damage to renal tubules by cisplatin often causes acute kidney injury (20-30%) and affects renal reabsorptive capacity including magnesium reabsorption, resulting in renal magnesium wasting and hypomagnesemia (40-100%)[4]. Furthermore, hypomagnesemia can worsen the nephrotoxicity by enhancing the renal accumulation of cisplatin via upregulation of OCT2 [34]. Therefore magnesium supplementation for prevention of hypomagnesemia might be beneficial in cisplatin treatment.

Most of the included studies were conducted in patients receiving high - dose cisplatin (>50 mg/m^2). Therefore, magnesium supplementation might be benefit in these patients, probably due to the significant decreases in glomerular filtration rate (GFR) and magnesium levels[35]. The administration of magnesium supplementation for prevention of CIN should be considered. Intravenous administration is preferred. A previous study showed that intravenous and oral administration were equivalent in terms of increasing in serum magnesium level but oral administration increased risk of gastrointestinal tract adverse effects[36].

The administration of intravenous magnesium supplementation before cisplatin-based chemotherapy showed the benefits in almost studies. One of the possible reasons is that cisplatin affects the kidney within 6 hours after cisplatin - based chemotherapy initiation. Urinary markers of proximal tubulotoxicity increased within 3 - 6 hours after the chemotherapy[37]. Some studies added oral magnesium after the first intravenous dose. However, there is no evidence directly compared the effect of intravenous magnesium alone to that of the addition of oral magnesium on CIN prevention.

The European Society of Clinical Pharmacy Special Interest Group on Cancer Care guideline suggested magnesium supplementation based on limited evidencev[38]. Our findings supported the suggestion abovementioned. In addition, we found that 8 to 20 mEq of intravenous magnesium should be supplemented without the increased risk of hypermagnesemia[17,22].

Some limitations of this study should be addressed. First, most included studies were observational studies which had high risk of bias. It may affect the credibility of our findings. Second, we included only 10 studies for meta-analysis. Therefore, statistical publication bias assessment could not be performed. However, based on our searches which included most of major databases including PubMed, Cochrane Library, Web of Science, Scopus, and EMBASE. In addition, we searched for grey literature in clinicaltrial.gov. Thus, we believe that our search was comprehensive to minimize publication bias. Third, included studies had different regimen for hydration to prevent nephrotoxicity which might affect our findings. Forth, most included studies did not provide the information regarding any co-medications affecting nephrotoxic effect including nonselective nonsteroidal anti-inflammatory drugs as well as other risk factors for nephrotoxicity. Last, most included studies did not report magnesium level data before and after treatment. Therefore, the magnesium level could not be used as a factor for subgroup analysis. Applying our findings should be done with cautions.

5. CONCLUSIONS

Our most updated findings support the use of magnesium supplementation as a pre - hydration to prevent CIN, especially for severe nephrotoxicity. Oncologists might consider adding 8 - 20 mEq magnesium in patients receiving a cumulative dose of ≥50 mg/m^2 of cisplatin. However, because of limited number of studies and their qualities. Further high-quality randomized controlled studies should be

conducted to confirm such effects.

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CONFLICT OF INTEREST

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REFERENCES

1. Pabla N, Dong Z. Cisplatin nephrotoxicity: Mechanisms and renoprotective strategies. Kidney Int. 2008;73:994-1007.
2. Prasaja Y, Sutandyo N, Andrajati R. Incidence of cisplatin-induced nephrotoxicity and associated factors among cancer patients in indonesia. Asian Pac J Cancer Prev. 2015;16:1117-22.
3. Yao X, Panichpisal K, Kurtzman N, Nugent K. Cisplatin nephrotoxicity: A review. Am J Med Sci. 2007;334:115-24.
4. Miller RP, Tadagavadi RK, Ramesh G, Reeves WB. Mechanisms of cisplatin nephrotoxicity. Toxins (Basel). 2010;2:2490-518.
5. Yamamoto Y, Watanabe K, Matsushita H, Tsukiyama I, Matsuura K, Wakatsuki A. Multivariate analysis of risk factors for cisplatin-induced nephrotoxicity in gynecological cancer. J Obstet Gynaecol Res. 2017;43:1880-6.
6. Hayati F, Hossainzadeh M, Shayanpour S, Abedi-Gheshlaghi Z, Beladi Mousavi SS. Prevention of cisplatin nephrotoxicity. J Nephropharmacol. 2016;5:57-60.
7. Kobayashi R, Suzuki A, Matsuura K, Yamada N, Nakano M, Deguchi T, et al. Risk analysis for cisplatin-induced nephrotoxicity during first cycle of chemotherapy. Int J Clin Exp Med. 2016;9:3635-41.
8. 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(7):e101902.
9. 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.
10. Hodgkinson E, Neville-Webbe HL, Coleman RE. Magnesium depletion in patients receiving cisplatin-based chemotherapy. Clin Oncol (R Coll Radiol). 2006;18:710-18.
11. Yamamoto Y, Watanabe K, Matsushita H, Tsukiyama I, Matsuura K, Wakatsuki A. The incidence of cisplatin-induced hypomagnesemia in cervical cancer patients receiving cisplatin alone. Yakugaku Zasshi. 2017;137:79-82.
12. Bell DR, Woods RL, Levi JA. cis-Diamminedichloroplatinum-induced hypomagnesemia and renal magnesium wasting. Eur J Cancer Clin Oncol. 1985;21:287-90.
13. Ashraf M, Scotchel PL, Krall JM, Flink EB. cis-Platinum-induced hypomagnesemia and peripheral neuropathy. Gynecol Oncol. 1983;16:309-18.
14. Saito Y, Okamoto K, Kobayashi M, Narumi K, Furugen A, Yamada T et al. Magnesium co-administration decreases cisplatin-induced nephrotoxicity in the multiple cisplatin administration. Life Sci. 2017;189:18-22.
15. Ashrafi F, Haghshenas S, Nematbakhsh M, Nasri H, Talebi A, Eshraghi-Jazi F, et al. The role of magnesium supplementation in cisplatin-induced nephrotoxicity in a rat model:no nephroprotectant effect. Int J Prev Med. 2012;3:637-43.
16. Solanki MH, Chatterjee PK, Xue X, Gupta M, Rosales I, Yeboah MM, et al. Magnesium protects against cisplatin-induced acute kidney injury without compromising cisplatin-mediated killing of an ovarian tumor xenograft in mice. Am J Physiol Renal Physiol. 2015;309:F35-47.
17. Willox JC, McAllister EJ, Sangster G, Kaye SB. Effects of magnesium supplementation in testicular cancer patients receiving cis-platin: a randomised trial. Br J Cancer. 1986;54:19-23.
18. Yamamoto Y, Watanabe K, Tsukiyama I, Yabushita H, Matsuura K, Wakatsuki A. Hydration with 15 mEq magnesium is effective at reducingthe risk for cisplatin-induced nephrotoxicity in patients receiving cisplatin (≥50 mg/m2) combination chemotherapy. Anticancer Res. 2016;36:1873-77.
19. 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.
20. Hirai S, Kaida S, Ito T, Hasebe S, Ueno M, Udagawa H, et al. Magnesium premedication prevents cisplatin-induced nephrotoxicity in patients with esophageal and hypopharyngeal cancer. Gan To Kagaku Ryoho. 2013;40:743-7.
21. Muraki K, Koyama R, Honma Y, Yagishita S, Shukuya T, Ohashi R, et al. Hydration with magnesium and mannitol without furosemide prevents the nephrotoxicity induced by cisplatin and pemetrexed in patients with advanced non-small cell lung cancer. J Thorac Dis. 2012;4:562-8.
22. Bodnar L, Wcislo G, Gasowska-Bodnar A, Synowiec A, Szarlej-Wcisło K, Szczylik C. Renal protection with magnesium subcarbonate and magnesium sulphate in patients with epithelial ovarian cancer after cisplatin and paclitaxel chemotherapy: A randomised phase II study. Eur J Cancer. 2008;44:2608-14.
23. Kimura T, Ozawa T, Hanai N, Hirakawa H, Suzuki H, Hosoi H, et al. Renal protective effect of a hydration supplemented with magnesium in patients receiving cisplatin for head and neck cancer. J Otolaryngol Head Neck Surg. 2018;47(1):10.
24. Konishi H, Fujiwara H, Itoh H, Shiozaki A, Arita T, Kosuga T, et al. Influence of magnesium and parathyroid hormoneon cisplatin induced nephrotoxicity in esophageal squamous cell carcinoma. Oncol Lett. 2018;15:658-64.
25. Oka T, Kimura T, Suzumura T, Yoshimoto N, Nakai T, Yamamoto N, et al. Magnesium supplementation and high volume hydration reduce the renal toxicity caused by

cisplatin-based chemotherapy in patients with lung cancer: a toxicity study. BMC Pharmacol Toxico. 2014;15:70.
26. 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.
27. Yamaguchi T, Uozu S, Isogai S, Hayashi M, Goto Y, Nakanishi T, et al. Short hydration regimen with magnesium supplementation prevents cisplatin-induced nephrotoxicity in lung cancer: a retrospective analysis. Support Care Cancer. 2017;25:1215-20.
28. The National Cancer Institute (NCI) of the National Institutes of Health (NIH). Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.2010 [cited 2019 April 30], Available from: http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf.
29. Higgins JPT, Savović J, Page MJ, Sterne JAC and the development group for RoB 2.0. Revised Cochrane risk of bias tool for randomized trials (RoB 2.0). 2019 [cited 2019 April 30]. Available from: https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2.
30. Sterne JAC, Higgins JPT, Elbers RG, BC R and the development group for ROBINS-I. Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I): detailed guidance. 2016 [cited 2019 April 30]. Available from: http://www.riskofbias.info.
31. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177-88.
32. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-60.
33. Harrach S, Ciarimboli G. Role of transporters in the distribution of platinum-based drugs. Front Pharmacol. 2015;6:85.
34. Yokoo K, Murakami R, Matsuzaki T, Yoshitome K, Hamada A, Saito H. Enhanced renal accumulation of cisplatin via renal organic cation transporter deteriorates acute kidney injury in hypomagnesemic rats. Clin Exp Nephrol. 2009;13:578-84.
35. Hartmann JT, Kollmannsberger C, Kanz L, Bokemeyer C. Platinum organ toxicity and possible prevention in patients with testicular cancer. Int J Cancer. 1999;83:866-9.
36. Martin M, Diaz-Rubio E, Casado A, López Vega JM, Sastre J, Almenarez J. Intravenous and oral magnesium supplementations in the prophylaxis of cisplatin-induced hypomagnesemia. Results of a controlled trial. Am J Clin Oncol. 1992;15:348-51.
37. Bunel V, Tournay Y, Baudoux T, De Prez E, Marchand M, Mekinda Z, et al. Early detection of acute cisplatin nephrotoxicity: interest of urinary monitoring of proximal tubular biomarkers. Clin Kidney J. 2017;10:639-47.
38. Launay-Vacher V, Rey JB, Isnard-Bagnis C, Deray G, Daouphars M, European Society of the art and recommendations from the European Society of Clinical Pharmacy Special Interest Group on Cancer Care. Cancer Chemother Pharmacol. 2008;61:903-9.