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

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Keywords:
magnesium, supplementation, cisplatin, nephrotoxicity

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/m²/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\textsuperscript{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\textsuperscript{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\textsuperscript{9}. The occurrence of CIN depends on the number of cycles, which reflects the cumulative dose of cisplatin\textsuperscript{10-13}. Some clinical studies have reported the advantage of magnesium supplementation in CIN prevention\textsuperscript{8,14-24} but some clinical studies showed no protective effects\textsuperscript{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.)\textsuperscript{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)\textsuperscript{29} for randomized trials and Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I)\textsuperscript{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\textsuperscript{31}. The pooled relative risk with its corresponding 95% confidence interval (95%Ct) was presented for the occurrence of nephrotoxicity, while the pooled mean difference (MD) with its corresponding 95%Ct 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\textsuperscript{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\textsuperscript{8,17-27} were included in qualitative synthesis. Of those, ten studies provided sufficient data to perform
| 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)⁹ | Japan | All type | Retrospective Study | NA | 67/334 | Various regimens | ≥ 60 mg/m² | 20 mEq MgSO₄ IV plus hydration plus mannitol plus furosemide | Hydration plus mannitol plus furosemide | Grade nephrotoxicity and ΔScr |
| Wilcox JC (1986)¹⁷ | UK | Testicular cancer | Randomized controlled trials | 29/33 | 8/9 | cisplatin, vinblastine, bleomycin | 20 mg/m² day 1 to 5 | 8 mmol MgSO₄ IV day 1 to 5 plus hydration then magnesium citrate 10 mmol oral lid daily 15 mEq MgSO₄ IV plus hydration day 1 then 5 mEq MgSO₄ IV day 2 and 3 | 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 cisplatin plus irinotecan or docetaxel cisplatin plus 5-fluorouracil | 50 mg/m² except irinotecan plus cisplatin 60 mg/m² | | Hydration | RIFLE criteria |
| Yoshida T (2014)¹⁹ | Japan | Thoracic malignancy | Retrospective Study | 64/65 | 161/335 | >60 mg/m² | 8 mEq MgSO₄ IV plus hydration plus mannitol | Hydration plus mannitol | Grade nephrotoxicity |
| Hiraiz S (2013)²⁰ | Japan | Esophageal and hypopharyngeal cancer | Retrospective Study | 64/66 | 10/13 | cisplatin plus 5-fluorouracil | 80 mg/m² | 20 mEq MgSO₄ 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/m² | 8 mEq MgSO₄ IV plus hydration plus mannitol plus furosemide | Hydration plus mannitol plus furosemide | ΔScr, ΔCrCl²⁸ |
| Bodnar L (2008)²² | Poland | Ovarian cancer | Randomized controlled trials | 53/54 | 20/20 | paclitaxel 135mg/m² IV over a 24-h on day 1 followed by 75mg/m² of IV infusion cisplatin on day 2 | 75 mg/m² | 5 g MgSO₄ IV plus prehydration then magnesium subcarbonate 500 mg oral lid | Placebo and hydration | ΔScr, ΔCrCl²⁸ |
| Kimura T (2018)²³ | Japan | Head and neck cancer | Retrospective Study | 62/62 | 56/65 | cisplatin plus 5-fluorouracil | 80 mg/m² | 20 mEq MgSO₄ IV plus hydration | Hydration | ΔCrCl²⁸ |
| 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)\(^{21}\) | 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 cisplatin, docetaxel, and 5-fluorouracil (DCF) regimen | 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 plus vinorelbine or pemetrexed or pemetrexed+ bevacizumab or irinotecan or etoposide or gemcitabine or irinotecan | 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 Terminology Criteria for Adverse Events (CTCAE), version 4.0
\(^{\#}\) Cockerill-Gault equation
meta-analysis\textsuperscript{8,19-27} because 2 studies\textsuperscript{17-18} reported different nephrotoxic-related outcome from ten studies (Figure 1). Nine studies were retrospective observational studies\textsuperscript{8,18,21,23,25-27}, whereas two studies were randomized controlled trials (RCTs)\textsuperscript{17,22} and one study was prospective observational study\textsuperscript{24}. All included studies were conducted in patients with solid tumors and receiving $\geq 50$ mg/m\textsuperscript{2}/cycle of cisplatin-based chemotherapy. Intravenous magnesium sulfate (MgSO\textsubscript{4}) administration (8-20 milliequivalence; mEq) prior to chemotherapy initiation was used as intervention of interest for eleven included studies\textsuperscript{17-27}. Only one study administered intravenous MgSO\textsubscript{4} after chemotherapy\textsuperscript{8}. Two studies also added oral magnesium supplementation afterwards\textsuperscript{17,22}. Four studies reported both grade of nephrotoxicity and changes in SCr and/or CrCl\textsuperscript{8,25-27}, while three studies reported only grade of nephrotoxicity\textsuperscript{19,20,24}. Three studies reported only changes in SCr or/and CrCl\textsuperscript{21-23}, and the other two studies reported other nephrotoxicity-related outcomes including urine N-acetyl- B-D-glucosaminidase (NAG) activity\textsuperscript{17} and Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease (RIFLE) criteria\textsuperscript{18}. The study characteristics of included studies were summarized in Table 1.

The quality of RCTs\textsuperscript{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\textsuperscript{17}. The other ten observational studies\textsuperscript{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 cycles. 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.](image)

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 MgSO₄ | 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)²¹, Saito Y (2017)²⁶, Yamaguchi T (2017)²⁷ |
| 20 mEq MgSO₄ | 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 MgSO₄ | 3 | 258/415 | 19/333 | 0.29 (0.19 to 0.45) | <0.001 | 0.0% | Yoshida T (2014)¹⁹, Konishi H (2018)²¹, Yamaguchi T (2017)²⁷ |
| **First cycle of chemotherapy** | | | | | | | |
| Any doses MgSO₄ | 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)²², Saito Y (2017)²⁶, Yamaguchi T (2017)²⁷ |
| 20 mEq MgSO₄ | 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 MgSO₄ | 3 | 265/438 | 9/85 | 0.19 (0.08 to 0.47) | <0.001 | 16.9% | Yoshida T (2014)¹⁹, Oka T (2014)²², Yamaguchi T (2017)²⁷ |
| **Any level of nephrotoxicity (All grades based on CTCAE version 4.0)** | | | | | | | |
| **All cycles of chemotherapy** | | | | | | | |
| Any doses MgSO₄ | 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)²¹, Saito Y (2017)²⁶, Yamaguchi T (2017)²⁷ |
| 20 mEq MgSO₄ | 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 MgSO₄ | 2 | 258/415 | 116/333 | 0.55 (0.33 to 0.91) | 0.019 | 51.2% | Yoshida T (2014)¹⁹, Konishi H (2018)²¹, Yamaguchi T (2017)²⁷ |
| **First cycle of chemotherapy** | | | | | | | |
| Any doses MgSO₄ | 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)²², Saito Y (2017)²⁶, Yamaguchi T (2017)²⁷ |
| 20 mEq MgSO₄ | 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 MgSO₄ | 3 | 265/438 | 131/335 | 0.63 (0.31 to 1.27) | 0.197 | 97.6% | Yoshida T (2014)¹⁹, Oka T (2014)²², Yamaguchi T (2017)²⁷ |

I/C: intervention/control, MgSO₄: 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; I²=0%) and the nephroprotective effect was likely to be dose-dependent⁸,¹⁹,²⁵-²⁷ (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; I²=55.7%), while that for the first cycle was 0.42 (95%CI 0.18 to 0.95; I²=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](image-url)  
**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.⁸,¹²-¹³,¹⁹,²³,²⁵-²⁷. 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; I²=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; I²=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; I²=0.0%) and -12.02 (95% CI -14.83 to -9.22; I²=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 (%I²) | Pooled studies |
|---------------|-------------------|------------------------------|-------------------------|---------|---------------------|----------------|
| **Increase of SCr** |                   |                              |                         |         |                     |                |
| All cycle     |                   |                              |                         |         |                     |                |
| Any doses MgSO₄ | 4                 | 129/142                      | -0.20                   | <0.001  | 60.1%               | Muraki K (2012)²¹, Bodnar L (2008)²², Saito Y (2017)²⁶, Yamaguchi T (2017)²⁷ |
| ≥20 mEq MgSO₄  | 2                 | 49/50                        | -0.23                   | 0.011   | 81.4%               | Bodnar L (2008)²², Saito Y (2017)²⁶ |
| 8 mEq MgSO₄    | 2                 | 80/92                        | -0.18                   | <0.001  | 20.4%               | Muraki K (2012)²¹, Yamaguchi T (2017)²⁷ |
| **First cycle** |                   |                              |                         |         |                     |                |
| Any doses MgSO₄ | 5                 | 220/487                      | -0.19                   | <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 MgSO₄  | 3                 | 116/384                      | -0.21                   | <0.001  | 81.5%               | Kidera (2014)⁸, Bodnar L (2008)²², Saito Y (2017)²⁶ |
| 8 mEq MgSO₄    | 2                 | 104/103                      | -0.16                   | <0.001  | 8.6%                | Oka T (2014)²⁵, Yamaguchi T (2017)²⁷ |
| **Decrease of CrCl** |                 |                              |                         |         |                     |                |
| All cycle     |                   |                              |                         |         |                     |                |
| Any doses MgSO₄ | 4                 | 125/145                      | -11.33                  | <0.001  | 0.0%                | Muraki K (2012)²¹, Bodnar L (2008)²², Kimura T (2018)³³, Saito Y (2017)²⁶ |
| ≥20 mEq MgSO₄  | 3                 | 105/115                      | -11.87                  | <0.001  | 29.3%               | Bodnar L (2008)²², Kimura T (2018)³³, Saito Y (2017)²⁶ |
| 8 mEq MgSO₄    | 1                 | 20/30                        | -11.42                  | <0.001  | NA                  | Muraki K (2012)²¹ |
| **First cycle** |                   |                              |                         |         |                     |                |
| Any doses MgSO₄ | 3                 | 93/91                        | -12.02                  | <0.001  | 0.0%                | Bodnar L (2008)²², Oka T (2014)²⁵, Saito Y (2017)²⁶ |
| ≥20 mEq MgSO₄  | 2                 | 49/50                        | -13.18                  | <0.001  | 0.0%                | Bodnar L (2008)²², Saito Y (2017)²⁶ |
| 8 mEq MgSO₄    | 1                 | 44/41                        | -11.71                  | <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 cisplatin33. 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/m²). Therefore, magnesium supplementation might be benefit in these patients, probably due to the significant decreases in glomerular filtration rate (GFR) and magnesium levels35. 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 effects36.

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 chemotherapy37. 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 evidencev38. 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 hypermagnesemia17,22.

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 caution.

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/m² 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.

6. ACKNOWLEDGEMENTS

The authors would like to acknowledge Mr. Perter Barton, Division of international Affairs and Language Development (DIALD), Naresuan University, Thailand, for their useful suggestions to the language and structure of the manuscripts.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethical approval

None to declare.

Article info:

Received June 24, 2019
Received in revised form November 29,2019
Accepted March 30, 2020

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