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Title

Relationship between magnesium dosage and the preventive effect on cisplatin-induced nephrotoxicity: meta-analysis and meta-regression analysis

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Abstract

Background: Cisplatin (CDDP) is an anticancer drug used to treat several types of cancer. CDDP-induced nephrotoxicity (CIN) is a serious adverse effect of CDDP treatment. Although magnesium sulfate (Mg) premedication has been proven to prevent CIN, the relationship between Mg dosage and its preventive effects on CIN are unknown. Therefore, we have evaluated this relationship using meta-analysis and meta-regression analysis to optimize cancer chemotherapies, including CDDP. **Methods:** We selected candidate studies, generated a forest plot to evaluate the preventive effects of Mg on CIN, and performed subgroup analyses. Moreover, a meta-regression analysis was conducted to reveal the relationship between Mg dosage and its preventive effects on CIN. **Results:** We identified 17 related studies and the total odds ratio (OR) of Mg premedication on CIN was 0.26 and the 95% confidence interval (95%CI) was 0.17–0.41 ($p < 0.00001$) although funnel plot suggested asymmetry. In subgroup analysis by forest plot, total OR with 95%CI of low Mg dosage administration (less than 10 mEq) and high Mg dosage administration (10 mEq or higher) was 0.35 (0.16–0.77, $p = 0.0169$) and 0.12 (0.07–0.21, $p < 0.0001$), respectively. In addition, meta-regression analysis was performed on Mg dosage and the OR of related studies, indicating a relationship between Mg dosage and OR ($p = 0.0349$). **Conclusion:** This study has revealed that premedication with Mg prevented CIN in a dose-dependent manner.

1 **Keywords**

2 Cisplatin; Magnesium; Cisplatin-induced nephrotoxicity; Meta-analysis; Meta-
3 regression analysis; Diuretic drugs

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1 **Introduction**

2 Cisplatin (cis-dichloro-diammine platinum, CDDP) is a highly potent anticancer drug
3 that binds to DNA and is widely used to treat several types of cancer [1, 2]. Although cancer
4 treatment options are increasing and becoming more diverse, CDDP remains the first-line
5 agent for the treatment of some carcinomas [3]. CDDP-induced nephrotoxicity (CIN) is one
6 of the most serious adverse effects in 30% of patients treated with CDDP and is a dose-
7 limiting toxicity of CDDP [4, 5].

8 Hydration and diuretics have been used as strategies to prevent CIN [6]. In addition,
9 premedication with magnesium sulfate (Mg) has been a promising preventive method for CIN
10 in recent years [7]. The mechanisms of CIN prevention by Mg include antioxidant effects and
11 changes in the expression of renal transporters that transport CDDP [8, 9]. Although the
12 preventive effect of Mg on CIN has been demonstrated, a suitable Mg dosage or dose-
13 dependent efficacy remains unknown.

14 Although a subgroup analysis in a previous meta-analysis evaluated the association
15 between each Mg dosage and preventive efficacy against CIN using forest plots [10], there
16 have been no reports on the relationship between Mg dosages and CIN prevention. The
17 assessment of the appropriate Mg dosage is important for improving CIN management.
18 Consequently, this study aimed to evaluate the preventive efficacy of intravenous Mg
19 premedication against CIN and the relationship between Mg dosage and CIN prevention to

optimize CDDP treatment.

Materials and methods

1. Data sources and search strategies

We identified related studies in the PubMed and Web of Science databases, and the following term was used for the search: “cisplatin magnesium” (the last search was performed on November 15, 2023). Thereafter, we selected clinical research articles written in English to evaluate the effects of Mg on CIN. Manuscript screening was conducted on two individuals (KO and YS).

2. Selection criteria

The selected articles satisfied the following inclusion criteria: 1) full-text articles, 2) intravenous administration of Mg, and 3) reporting the number of patients experiencing CIN with or without Mg premedication and statistically comparing the difference. Studies with the following conditions were not considered for selection: 1) oral Mg administration alone; 2) non-intravenous administration of CDDP (e.g., intraperitoneal injection); 3) research targeting children; 4) case reports or review articles; and 5) studies designed using meta-analysis, pooled analysis, or a medical database.

3. Data extraction

Two independent authors (KO and YS) extracted the following data according to the

inclusion criteria: name of the first author, year of publication, CDDP dose, Mg dose, cancer type, primary endpoint, CIN definition, concomitant use of diuretic drugs, and number of patients. If the definition of CIN was not provided in detail in the paper, we made a judgement based on the results of the report. Quality assessment of the candidate studies was performed using the Newcastle-Ottawa scale (NOS) [11]. Each study was evaluated based on this assessment scale (case-control study and cohort study) and assigned a score ranging from 0 to 9. The scores were classified as follows: 0–3, very high risk of bias; 4–6, high risk of bias; and 7–9, high quality.

4. Statistical analysis

Data were analyzed using R software (R Foundation for Statistical Computing, Vienna, Austria) with the meta and metafor packages. The primary endpoint was defined as the evaluation of the incidence of CIN with and without Mg premedication using a forest plot. The secondary endpoint was to assess the relationship between CIN prevention and Mg dosage or diuretic use. The characteristics of the included studies were summarized using odds ratios (ORs) and 95% confidence interval (95%CI). Forest plots were generated using the fixed-effects model with Mantel-Haenszel (M-H) methods or the random-effects model with inverse variance (IV) methods, and p value < 0.05 was considered to indicate statistical significance. In the forest plot, events indicate the occurrence of CIN. We evaluated heterogeneity among the studies using the Cochran Q test and the I^2 index; Cochran Q test p

value < 0.1 and $I^2 > 50\%$ were correlated with high heterogeneity. Fixed- and random-effects models were used for low and high heterogeneity, respectively. The meta-regression analysis used candidate papers with fixed Mg dosages, as shown in the bubble plot. Publication bias was examined using a funnel plot (visual inspection), Egger's test [12], and Peters' test [13]. An asymmetric funnel plot and p value < 0.1 correlated with potential publication bias.

Results

1. Data search

A literature search of PubMed and Web of Science databases yielded 416 and 384 reports, respectively. After an in-depth evaluation, 17 papers were extracted as candidates (Figure 1). Table 1 shows the characteristics of the eligible studies [4, 6, 7, 14–27]. The report by Miyoshi *et al.* was a singular multicenter study, while the others were performed at a single institution [20]. Of the 17 included studies, 9 studies attained a score of 7 using the NOS methods, 7 studies had a score of 6, and 1 study a score of 5.

2. The effect of Mg premedication on CIN incidence

The effect of Mg premedication on the incidence of CIN was analyzed using 17 candidate articles from a forest plot. The total OR with 95%CI was 0.26 (0.17–0.41, $p < 0.0001$), and I^2 was 65% ($p < 0.01$) (Figure 2a), suggesting that the Mg premedication significantly prevented CIN. Additionally, a funnel plot was created using candidate reports,

which showed asymmetry (Figure 2b). Moreover, Egger's and Peters' tests resulted in $p = 0.0155$ and 0.1180 , respectively, suggesting that publication bias may exist among these reports.

3. Evaluation of CIN prevention in different Mg dosages

A subgroup analysis was performed on Mg dosage to clarify the dose-dependence of the CIN-preventive efficacy of Mg because high heterogeneity and publication bias were suggested. Total OR with 95%CI of a low Mg dosage administration (less than 10 mEq) and a high Mg dosage administration (10 mEq or higher) was 0.35 ($0.16-0.77$, $p = 0.0169$) and 0.12 ($0.07-0.21$, $p < 0.0001$), and I^2 was 58% ($p = 0.03$) and 0% ($p = 0.83$), respectively (Figure 3a and 3b). The study by Minzi *et al.* was excluded because it could not be determined whether Mg was a hydrate or not; therefore, conversion to mEq was impossible [19]. In addition, a meta-regression analysis performed on Mg dosages and the OR of related papers indicated a relationship between Mg dosage and OR ($p = 0.0349$) (Figure 3c). The negative slope in Figure 3c shows that Mg premedication can prevent CIN in a dose-dependent manner.

4. Evaluation of CIN prevention in different prophylactic diuretic drugs

To assess the influence of prophylactic diuretic drugs, which is also an effective CIN preventive method [6], on the Mg prophylaxis, we performed subgroup analysis focusing on the prophylactic use of furosemide, mannitol, and these combinations. In the groups administered furosemide alone and combination with mannitol, the total OR with 95%CI was

0.13 (0.05–0.31, $p < 0.0001$) and 0.13 (0.06–0.28, $p < 0.0001$), respectively, suggesting that the prophylactic use of furosemide was effective. On the other hand, in a group using mannitol alone, the OR was found to be 0.29 and 95%CI was 0.03–3.43 ($p = 0.2111$), suggesting that no effect of Mg on preventing CIN was observed (Table 2).

Discussion

In this study, we have evaluated the effect of Mg premedication on CIN by meta-analysis and found that Mg significantly ameliorated these symptoms. However, the funnel plot showed asymmetry and the results were statistically significant in the Egger test, indicating the possibility of publication bias among the candidate papers. In addition, no papers reported negative results in the lower right corner of the funnel plot because the CIN preventive effect of Mg is widely known and few reports with negative results have been published in the literature. In particular, because the primary endpoint of this meta-analysis was the evaluation of intravenous Mg premedication against CIN, studies with positive results were mainly extracted as candidate papers, and those with negative results, such as the report by Tanaka *et al.* (OR: 1.95) [24], were difficult to extract. Moreover, the asymmetry of the funnel plot might be due to the similarity in the population of each candidate study due to the exclusion criteria used in this study, such as childhood cancer or non-intravenous administration of CDDP.

As a subgroup analysis, forest plots were created for low (less than 10 mEq) and high (10 mEq or more) Mg premedication separately, because high heterogeneity and publication bias were suggested, and both were found to have preventive effect on CIN, which was in line with a previous meta-analysis [10]. However, forest plots could not be used to determine the dose-dependent preventive efficacy of Mg. Therefore, we conducted a meta-regression analysis and found that a higher Mg dosage was more effective in preventing CIN. This study is the first to clarify the relationship between Mg dosage and CIN prevention, and the results are clinically useful. The optimal dose of Mg for CIN prevention may be 15–20 mEq because these dosages did not cause other side effects and did not change serum magnesium levels [7, 18], although high-dose administration of Mg can cause hypermagnesemia [28].

CIN is caused by the renal accumulation of CDDP, which is taken up by organic cation transporter 2 (OCT2) and copper transporter 1 (CTR1) and excreted by multidrug and toxin extrusions (MATEs) [29]. We previously showed that the mechanism underlying the preventive effect of Mg is a reduction in renal platinum accumulation due to a decrease in the expression levels of OCT2 and CTR1 and an increase in MATE1 in vivo [9, 30]. It has also been shown that halving the dose of Mg has fewer effects on OCT2 and platinum accumulation, reducing the CIN attenuation effect [9]. These results are consistent with the outcomes obtained in this study. Future studies are required to determine the optimal dose of Mg.

Diuretic drugs promote the excretion of CDDP from the kidney, which can act as CIN prophylaxis [6]. A subgroup analysis focusing on concomitant diuretic drugs showed that the concomitant use of furosemide did not affect the CIN-preventive efficacy of Mg, although mannitol alone could negate its efficacy. Previous meta-analysis has shown that mannitol is useful for grade ≥ 3 CIN prevention in ≤ 75 mg/m² CDDP treatment [31], and it is widely used in clinical [4, 7, 18]. We consider the large variation and high heterogeneity in a forest plot to be due to the high OR reported by Tanaka *et al.* (Table 2) caused the results.

In the candidate studies, there were some reports that defined CIN as grade ≥ 1 for serum creatinine level by Common Terminology Criteria for Adverse Events version (CTCAE v) 4.0 or 4.1. In these CTCAE versions, the evaluation of serum creatinine levels was based not only on reference values but also on changes from baseline, and the assessment of variance from baseline in grade 1 was deleted from version 5.0. In our meta-analysis, it is possible that some patients were diagnosed with grade 1 CIN by relative serum creatinine variation using CTCAE v4.0, or 4.1, which was not classified by version 5.0. Therefore, it is important to analyze this using a unified definition of CIN.

We selected only reports evaluating the intravenous administration of Mg in this study because oral administration of Mg causes more adverse events, such as mild gastrointestinal symptoms than intravenous administration [32]. Oral magnesium oxide is generally administered to manage constipation and is frequently used in CDDP-containing

1 treatments. However, because of its poor bioavailability, it is necessary to adjust its dosage
2 depending on the nature of the stool [33], we consider that oral Mg administration is not
3 suitable for CIN prevention.

4 This study has some limitations. First, we did not evaluate the detailed methods of
5 hydration. Oka *et al.* reported that the preventive effect of hydration on CIN varies depending
6 on the volume [21]; thus, an evaluation focusing on the hydration volume is necessary.
7 Second, since all of the candidate studies, except for the report by Minzi *et al.* [19], were
8 conducted in Japan, and the meta-regression analysis included only Japanese studies despite
9 their worldwide use [34], the obtained results may be limited to Japan. Third, although CIN is
10 CDDP dose-dependent [5], its dosage varied among the evaluated studies. Finally, the patient
11 background, definition of CIN, and primary endpoint differed between studies, and the factors
12 associated with CIN, such as complications (diabetes and hypertension) and Oct2 gene
13 polymorphisms [5], were also not evaluated.

14 In conclusion, our meta-analysis revealed that Mg premedication prevents CIN, and
15 the meta-regression analysis showed that its preventive effect can be dose-dependent. This
16 study provides important findings for appropriate management of CIN and contributes to the
17 establishment of clinical evidence. Therefore, it is necessary to verify the Mg dose-dependent
18 efficacy in future prospective clinical studies.

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3

4 **Author contribution**

5 KO, YS, and AY participated in this study. KO and YS conducted the study and
6 performed data analysis. KO, YS, AY, KN, and MK wrote or contributed to writing the
7 manuscript.

8

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11 commercial, or non-profit sectors.

12

13 **Conflict of Interest Disclosure Statement**

14 Authors declare no competing interest.

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16 **Data availability**

17 The datasets generated and/or analyzed in the current study are available from the
18 corresponding author upon reasonable request.

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Table 1 Characteristics of eligible studies

Study (Year)	Country	CDDP (mg/m ²)	Mg (mEq)	Cancer type	Primary endpoint	CIN definition	Diuretics	NOS
Aoyama T <i>et al.</i> (2020) ^[14]	Japan	50–80	20	Gastric	Evaluate short hydration	SCr increase of > 0.3 mg/dl or ≥ 1.5 times	Furosemide	7
Kidera Y <i>et al.</i> (2014) ^[15]	Japan	60–105	20	Several	Mg effect	Grade 2 $\geq$ of SCr in CTCAE v4.0	Combination	7
Kimura T <i>et al.</i> (2018) ^[16]	Japan	80	20	Head and neck	Mg effect	CCr decrease of $\geq 20\%$	Furosemide	6
Konishi H <i>et al.</i> (2018) ^[17]	Japan	70–80	8	Esophageal	Mg effect	Grade 1 $\geq$ in CTCAE v4.0 ^a	Combination	7
Kubo Y <i>et al.</i> (2019) ^[18]	Japan	40–70	20	Esophageal	Mg effect	Grade 2 $\geq$ of SCr in CTCAE v4.0	Mannitol	7
Minzi OMS <i>et al.</i> (2020) ^[19]	Tanzania	≥ 50 mg/body	1 g	Several	Mg·Ca·K effect	SCr increase of ≥ 1.5 times	unknown	7
Miyoshi T <i>et al.</i> (2020) ^[20]	Japan	60–80	several	Several	Risk factor	Grade 1 $\geq$ of SCr in CTCAE v4.0	several	6
Muraki K <i>et al.</i> (2012) ^[6]	Japan	75	8	Lung	Mg effect	Grade 1 $\geq$ of SCr in CTCAE v4.0	Combination	7
Oka T <i>et al.</i> (2014) ^[21]	Japan	75–80	8	Several	Mg effect	Grade 1 $\geq$ in CTCAE v4.0 ^a	Combination	5
Saito Y <i>et al.</i> (2017) ^[7]	Japan	75	20	Head and neck	Mg effect	Grade 2 $\geq$ of SCr in CTCAE v4.0	Mannitol	7

Sakaida E <i>et al.</i> (2016) ^[22]	Japan	60–80	5	Several	Evaluate short hydration	Grade 1 $\geq$ of SCr in CTCAE v4.0	several	6
Sugisaki T <i>et al.</i> (2022) ^[23]	Japan	70–80	20	Esophageal	Mg effect	Grade 2 $\geq$ of SCr in CTCAE v5.0	Furosemide	7
Tanaka M <i>et al.</i> (2018) ^[24]	Japan	60–80	8	Several	Evaluate short hydration	Grade 1 $\geq$ of SCr in CTCAE v4.0	Mannitol	6
Yamaguchi T <i>et al.</i> (2016) ^[25]	Japan	52.7–83.1	8	Lung	Evaluate short hydration	Grade 1 $\geq$ of SCr in CTCAE v4.0	several	6
Yamamoto Y <i>et al.</i> (2015) ^[26]	Japan	40	15	Cervical	Mg effect	RIFLE criteria class R	Furosemide rescue	7
Yamamoto Y <i>et al.</i> (2016) ^[27]	Japan	≥ 50	15	Several	Mg effect	RIFLE criteria class R	Furosemide rescue	6
Yoshida T <i>et al.</i> (2014) ^[4]	Japan	60–80	8	Several	Mg effect	Grade 2 $\geq$ of SCr in CTCAE v4.0	Mannitol	6

^a: no detailed description

CDDP, cisplatin; Mg, magnesium sulfate; CIN, CDDP-induced nephrotoxicity; SCr, serum creatinine; CTCAE v, Common Terminology Criteria for Adverse Events version; CCr, creatinine clearance; NOS, Newcastle-Ottawa scale score.

Table 2 Subgroup analysis of diuretic drugs

Subgroup	Number of studies	OR	95%CI	I ²	Meta-analysis model
Furosemide	3	0.13	0.05–0.31	0%	Fixed-effects model
Mannitol	4	0.29	0.03–3.43	80%	Random-effects model
Furosemide + Mannitol	4	0.13	0.06–0.28	0%	Fixed-effects model

OR, odds ratio; 95%CI, 95% confidence interval

Fig. 1

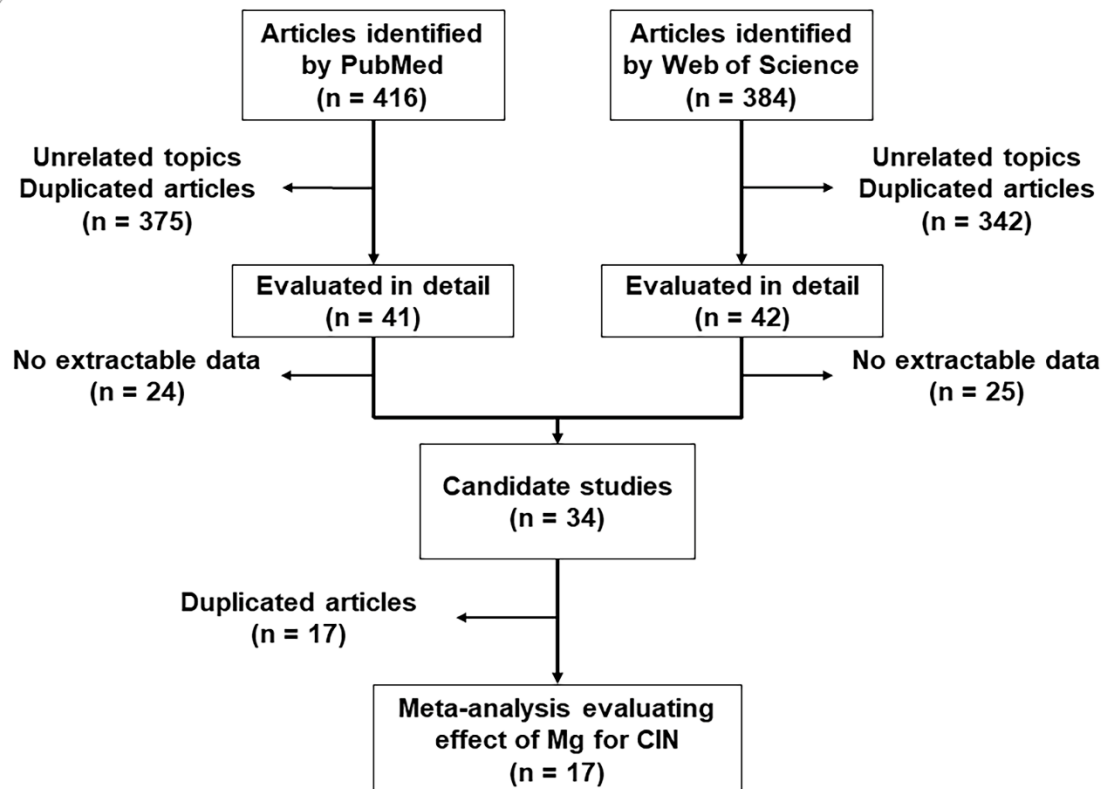


Fig. 1 Flow diagram of the study selection.

Fig. 2a

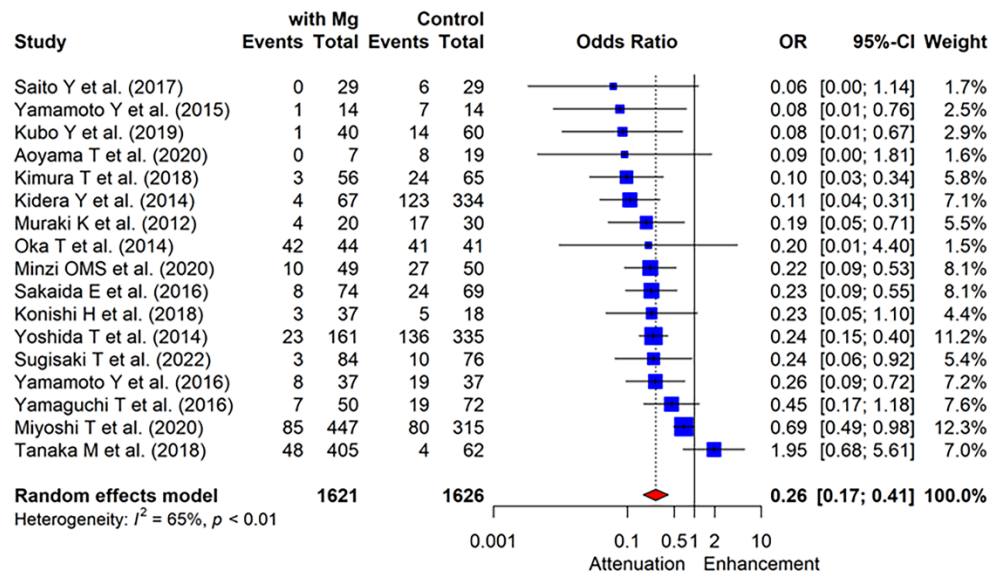


Fig. 2b

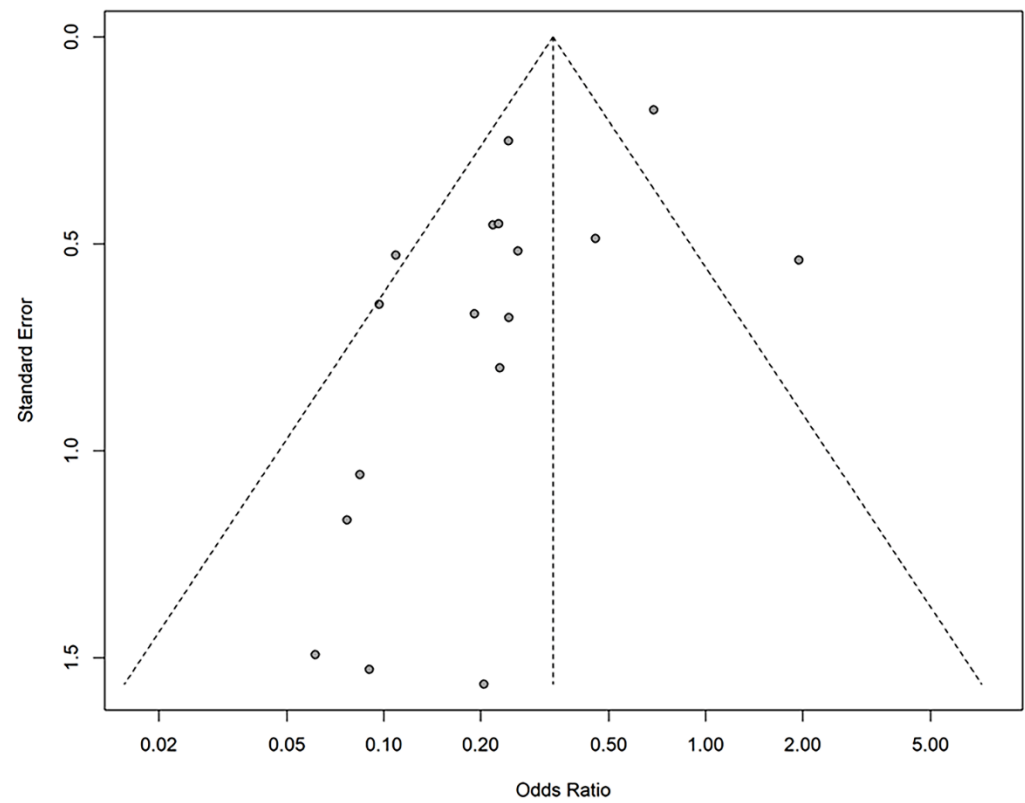


Fig. 2 The effect of Mg premedication on CIN. (a) Forest plot for assessing the effect of Mg on OR in patients with CDDP treatment. “Events” means CIN occurrence. I^2 indicates heterogeneity. (b) Funnel plots evaluated candidate studies.

Fig. 3a

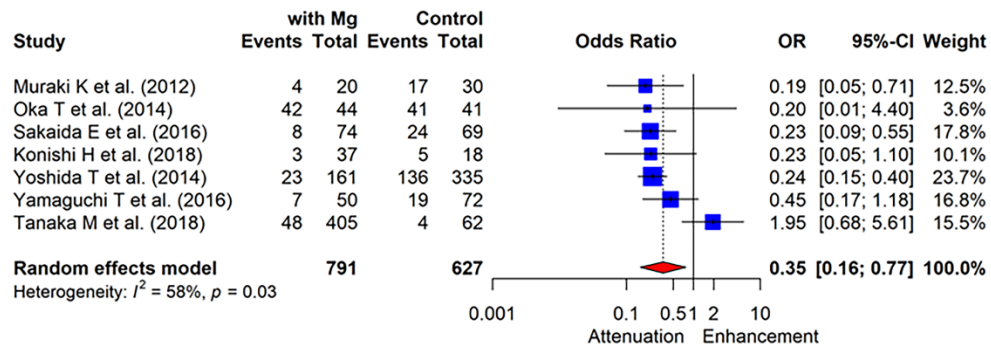


Fig. 3b

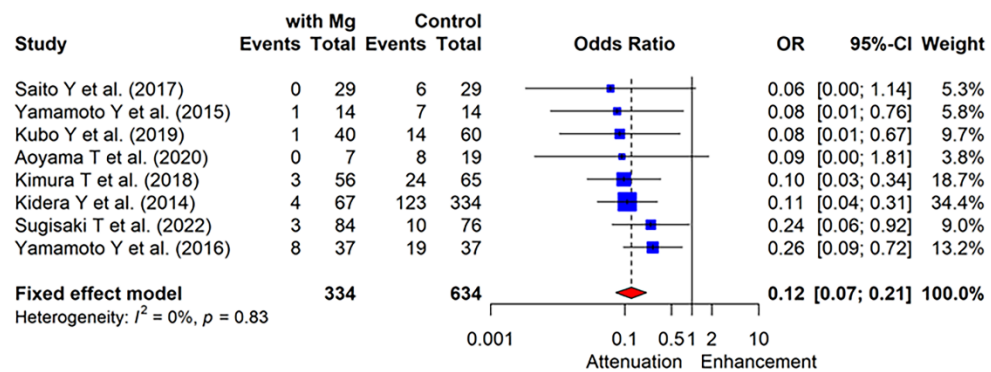


Fig. 3c

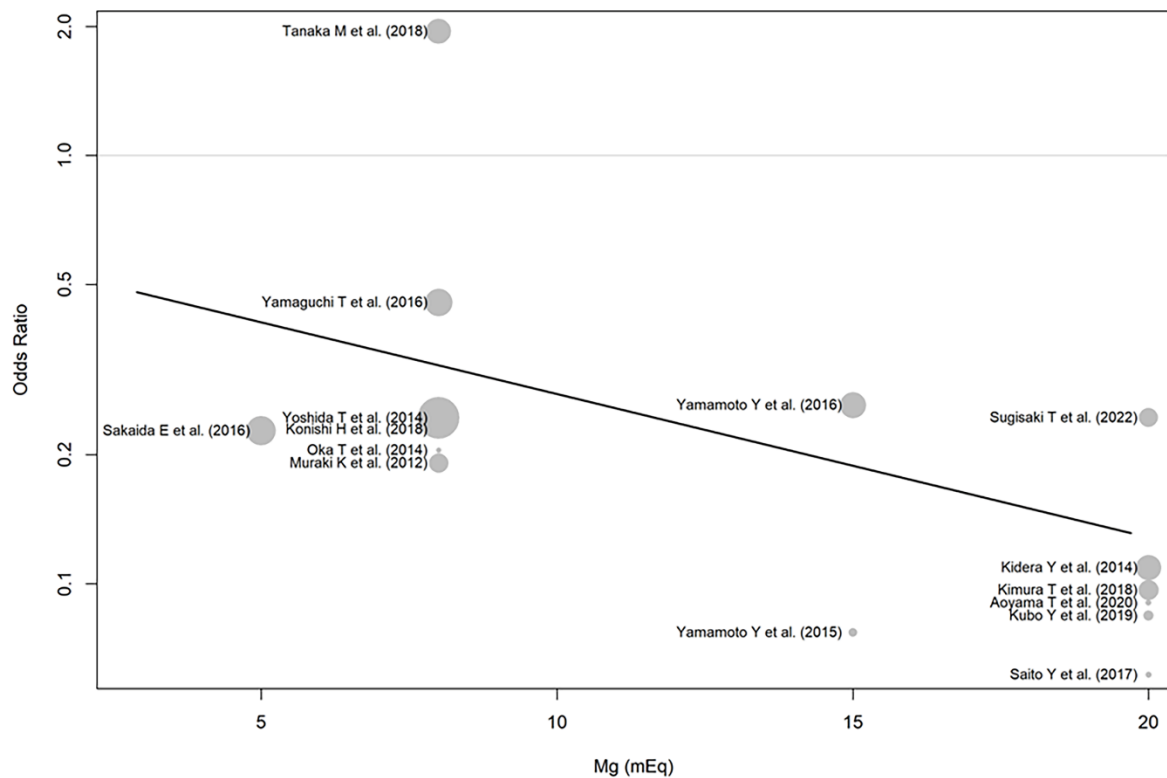


Fig. 3 The effect of low and high Mg dosage on CIN in a forest plot and the relationship between Mg dosage and preventive effect for CIN in meta-regression analysis. Forest plots assessing the effect of (a) low Mg dosage administration (less than 10 mEq) and (b) high Mg dosage administration (10 mEq or higher) on OR in patients with CDDP treatment. “Events” means CIN occurrence. I^2 indicates heterogeneity. (c) Meta-regression analysis evaluated the relationship between Mg dosage (mEq) and OR of each candidate study.