

Preventive Effect of 20 mEq and 8 mEq Magnesium Supplementation On Cisplatin-Induced Nephrotoxicity: A Propensity-Score Matched Analysis

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Abstract

Purpose

The protective effect of magnesium (Mg) supplementation against cisplatin (CDDP)-induced nephrotoxicity has been widely described; however, the optimal dose of Mg supplementation is unclear. The aim of this study was to investigate whether 20 mEq of Mg supplementation is more effective than 8 mEq Mg in preventing CDDP-induced nephrotoxicity, as well as the associated risk factors, in cancer patients treated with CDDP-based chemotherapy.

Methods

Pooled data of 272 patients receiving 20 mEq or 8mEq Mg supplementation to CDDP-based chemotherapy from a multicenter, retrospective, observational study were compared using propensity score matching. Separate multivariate logistic regression analyses were used to identify the risk factors for renal failure induced by each treatment dose.

Results

There was no significant difference in the incidence of CDDP-induced nephrotoxicity between the 8 mEq and 20 mEq groups (18.4% vs. 20.6%, $P = 0.760$). There was also no significant difference in the severity of nephrotoxicity, elevated serum creatinine levels, and decreased estimated creatinine clearance levels between the two groups. Cardiac disease and albumin levels were identified as independent risk factors for CDDP-induced nephrotoxicity.

Conclusion

We did not find an advantage of 20 mEq over 8 mEq Mg supplementation in terms of a preventive effect against CDDP-induced nephrotoxicity. The optimal dose of Mg supplementation for the prevention of CDDP-induced nephrotoxicity remains unknown, and further studies are warranted.

Introduction

Cisplatin (cis-dichlorodiamineplatinum II, CDDP) is one of the most widely used anticancer agents, representing a key drug in the treatment of several solid cancers [1]. However, CDDP-induced nephrotoxicity is a major dose-limiting factor that can influence the therapeutic efficacy [2, 3]. Renal dysfunction often causes a delay in or discontinuation of chemotherapy; therefore, it is important to minimize the incidence and severity of nephrotoxicity. Previous studies have shown that CDDP-induced nephrotoxicity can be prevented or reduced by lowering the concentration of CDDP and shortening the duration of CDDP exposure to the proximal tubules [4]. Several other strategies have been reported to prevent CDDP-induced nephrotoxicity, including high-volume hydration with at least 2 L of isotonic saline, forced diuresis with furosemide or mannitol, dose fractionation, and slower infusion [5–8].

Hypomagnesemia is another well-known adverse effect in patients receiving CDDP-based chemotherapy, which has been reported to occur in approximately 90% of patients receiving CDDP [9]. CDDP-induced hypomagnesemia and hypocalcemia have been suggested to be caused by damage to the renal tubular cells and calcium/magnesium (Mg)-sensitive receptors [9, 10]. Hypomagnesemia has also been recognized as a risk factor for impaired recovery of renal function in patients with severe acute kidney injury (AKI) [11]. Previous studies have shown that Mg supplementation during CDDP-based chemotherapy correlated with the prevention of CDDP-induced nephrotoxicity [12–14]. However, these studies have used varying doses of Mg supplementation, demonstrating that 8 mEq [15–17], 20 mEq [18, 19], and 40 mEq [12] of intravenous Mg supplementation all had preventive effects against CDDP-induced nephrotoxicity. Mg supplementation is most frequently administered at a dose of 8 mEq according to the National Comprehensive Cancer Network (NCCN) order template and/or the results of studies in Japan [15–17]. However, Hase et al. [19] reported that 20 mEq of Mg supplementation with a short hydration regimen was safe and feasible for patients with lung cancer receiving CDDP-based chemotherapy. Although the protective effect of Mg supplementation has been described in several studies, the optimal dose remains unclear. Mg supplementation should be kept to a necessity minimum, as there is concern that renal dysfunction may lead to hypermagnesemia. In our previous study reporting the risk factors for CDDP-induced nephrotoxicity [20], cardiac disease, hypoalbuminemia, non-Mg supplementation, hypertension, and high dose CDDP were extracted as risk factors.

Therefore, in this study, we investigated whether 20 mEq of Mg supplementation is more effective than 8 mEq of Mg in preventing CDDP-induced nephrotoxicity, as well as the associated risk factors, in cancer patients treated with CDDP-based chemotherapy, based on a pooled dataset of our previous study [20].

Methods

Setting and patients

The study design, including patient enrollment, data collection, and treatment, was described previously [20]. In brief, this multicenter, retrospective, observational study was conducted from spring 2014 to September 2016 in five hospitals affiliated with the National Hospital Organization in Kyushu, Japan. We analyzed the pooled data of 345 patients in this study [20]. This study was approved by the Institutional Review Board of each hospital. All patients were treated in accordance with the principles outlined in the Declaration of Helsinki. Accumulated patient data were used after allowing patients to refuse to participate using an opt-out form. The requirement for informed consent was waived because of the retrospective nature of the study. Patients with solid cancer, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, and those who had received Mg supplementation to CDDP-based therapy were eligible for inclusion in the present study. The exclusion criteria were prior CDDP-based chemotherapy or creatinine clearance (CLcr) < 60 mL/min immediately prior to CDDP administration.

Data collection

All data were collected from the medical records at each hospital. Information on sex; age; ECOG PS; cancer stage; primary cancer site; comorbidities (cardiac disease, diabetes mellitus, hypertension); and hematological, biochemical, and chemotherapeutic regimens (i.e., co-administered anticancer drugs, CDDP dosage, hydration volume, Mg supplementation, diuretics) was collected. We defined 2.5 L hydration within approximately 4.5 h

as short hydration [13] and other hydration methods (> 2.5 L) as the conventional high-volume hydration. In this study, all patients received conventional high-volume hydration. Cardiac disease was defined as a history of angina, myocardial infarction, atrial fibrillation, arrhythmia, or valvular disease. The medical records of all patients were retrospectively reviewed to confirm the diagnosis of diabetes and high blood pressure.

To evaluate nephrotoxicity, the increase in serum creatinine (SCr) was calculated using the maximum value based on an enzymatic method within 2 weeks of CDDP-based chemotherapy. For most patients, SCr was measured at least once every 2 weeks. CLcr was calculated using the Cockcroft-Gault equation [21]. CDDP-induced nephrotoxicity was defined as an increase in SCr after CDDP-based chemotherapy of at least one grade higher than the previous measure, using the Common Terminology Criteria for Adverse Events (CTCAE ver. 4.0) for AKI. Although there are two grading systems for the criteria of renal failure, the 'AKI of renal and urinary disorders' category and the 'creatinine increased' of the investigations category, we adopted the AKI, the evaluation criteria based on the baseline value of creatinine before chemotherapy for each patient; this was in line with our previous report [20].

Statistical analysis

Patient characteristics and incidence of nephrotoxicity were summarized using descriptive statistics or contingency tables, and were compared using Student's t-test and the Chi-square test.

Propensity score matching (PSM) was used to reduce bias and balance the characteristics between the 8 mEq and 20 mEq Mg supplementation groups. The propensity scores were calculated using a logistic regression model. Patients were matched for variables at a 1:1 ratio using a caliper width of 0.2 of the standard deviation from the propensity score logit.

Additionally, to assess independent risk factors for nephrotoxicity, we used multivariate logistic regression to control for the potentially confounding roles of age, sex, Mg dosage, cardiac disease, hypertension, and CDDP dosage. Inclusion of variables in the model was based on existing knowledge of risk factors for nephrotoxicity and the literature [18, 20, 22, 23].

A two-sided P value of < 0.05 was considered statistically significant. All statistical analyses were performed using JMP 14.3.0 (SAS Institute, Cary, NC, USA).

Results

Characteristics of patients

Of the 345 eligible patients, 272 patients matched by PSM were analyzed: 136 received 8 mEq of Mg supplementation and 136 received 20 mEq of Mg supplementation. The patients' baseline characteristics, including sex; age; the frequencies of stage IV, cardiac disease, diabetes, and hypertension; albumin; potassium; and CDDP dose, are shown in Table 1. There were no significant differences in these characteristics between the two groups after PSM.

Table 1
Patient characteristics

Characteristics	Before propensity score matching						After propensity score matching					
	8 mEq		20 mEq		P-value	8 mEq		20 mEq		P-value		
	n	%	n	%		n	%	n	%			
Sex	male	142	77.2	123	76.4	0.899	107	78.7	101	74.3	0.475	
	female	42	22.8	38	23.6		29	21.3	35	25.7		
Age, years	< 63	85	46.2	88	54.7	0.131	64	47.1	68	50.0	0.716	
	≥ 63	99	53.8	73	45.3		72	52.9	68	50.0		
Stage IV	yes	91	49.5	89	55.3	0.331	70	51.5	62	45.6	0.396	
	no	93	50.5	72	44.7		66	48.5	74	54.4		
Cardiac disease	yes	17	9.2	12	7.5	0.567	12	8.8	12	8.8	1.000	
	no	167	90.8	149	92.5		124	91.2	124	91.2		
Diabetes mellitus	yes	19	10.3	17	10.6	1.000	17	12.5	14	10.3	0.703	
	no	165	89.7	144	89.4		119	87.5	122	89.7		
Hypertension	yes	45	24.5	50	31.1	0.185	33	24.3	32	23.5	1.000	
	no	139	75.5	111	68.9		103	75.7	104	76.5		
Albumin, g/dL	≤ 3.9	101	54.9	80	49.7	0.387	69	50.7	59	43.4	0.274	
	> 3.9	83	45.1	81	50.3		67	49.3	77	56.6		
K, mEq/L	≥ 4.3	72	39.1	63	39.1	1.000	47	34.6	51	37.5	0.705	
	< 4.3	112	60.9	98	60.9		89	65.4	85	62.5		
CDDP dose, mg/m ²	≥ 75	99	53.8	115	71.4	> 0.001	89	65.4	90	66.2	1.000	
	< 75	85	46.2	46	28.6		47	34.6	46	33.8		
Number of cycles	1	23	12.5	25	15.5	0.439	14	10.3	17	12.5	0.703	
	≥ 2	161	87.5	136	84.5		122	89.7	119	87.5		

The baseline characteristics of all eligible patients before PSM are summarized in Table S1 of Online Resource 1. The details of the delivery of CDDP-based chemotherapy and diuretics are summarized in Table S2 of Online Resource 1. All patients received conventional high-volume hydration to prevent CDDP-induced nephrotoxicity.

Incidence of nephrotoxicity

The PSM-based incidence of nephrotoxicity after chemotherapy is shown in Fig. 1. The incidence of nephrotoxicity did not significantly differ between the 8 mEq and 20 mEq groups (18.4% vs. 20.6%, P = 0.76).

Severity of nephrotoxicity

The proportion of patients with a grade 2 or higher elevation in creatinine after CDDP-based chemotherapy was 2.9% and 3.7% in the 8 mEq group and 20mEq group, respectively. There was no significant difference in the severity of nephrotoxicity according to CTCAE grading between the two groups (Table 2).

Table 2
Severity of nephrotoxicity

	8 mEq		20 mEq		P-value
Severity grade	n = 136		n = 136		
	n	%	n	%	
Grade 0	111	81.6	108	79.4	0.926
Grade 1	21	15.4	23	16.9	
Grade 2	3	2.2	3	2.2	
Grade 3	1	0.7	2	1.5	

Changes in SCr and CLcr in all subsequent cycles

Figure 2 shows that there were no significant differences in the change in SCr (Δ SCr; maximum SCr – baseline SCr) and CLcr (Δ CLcr; maximum CLcr – baseline CLcr) between the two Mg supplementation dose groups in all subsequent cycles (P = 0.68 and P = 0.84, respectively).

Risk factors for CDDP-induced nephrotoxicity

The results of the univariate and multivariate logistic regression analyses of the risk factors for nephrotoxicity are shown in Table 3. Only cardiac disease and an albumin level below 3.9 g/dL were identified as independent risk factors for CDDP-induced nephrotoxicity.

Table 3
Risk factors for cisplatin-induced nephrotoxicity

	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Mg (mEq)				
20 vs. 8	1.151 (0.631–2.099)	0.760	1.099 (0.590–2.065)	0.766
Sex				
male vs. female	1.407 (0.662–2.990)	0.471	1.459 (0.669–3.184)	0.342
Age (years)				
≥63 vs. <63	0.974 (0.534–1.775)	1.000	0.612 (0.307–1.222)	0.164
Cardiac disease				
yes vs no	2.782 (1.144–6.762)	0.029	2.753 (1.039–7.290)	0.042
Hypertension				
yes vs. no	1.682 (0.870–3.254)	0.150	1.670 (0.798–3.496)	0.174
Albumin (g/dL)				
≤3.9 vs. >3.9	1.962 (1.048–3.674)	0.046	2.214 (1.133–4.325)	0.020
CDDP dose (mg)				
≥75 vs. <75	1.771 (0.894–3.508)	0.109	1.548 (0.766–3.130)	0.224
Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio.				

Discussion

Several studies have shown that intravenous Mg supplementation has preventive effects against CDDP-induced nephrotoxicity [13, 15–19, 24]. The dosage of Mg supplementation has varied widely in previous studies, ranging from 8 to 40 mEq [12, 13, 15–19, 24]. The NCCN has developed chemotherapy order templates for CDDP-based regimens, which consist of mannitol and 8 mEq Mg supplementation for the prevention of renal toxicity in cancer care, and this strategy has been adopted worldwide. Although some reports indicate the benefit of Mg supplementation at higher doses such as 20 mEq [18, 19] and 40 mEq [12], the optimal Mg supplementation dose for the prevention of CDDP-induced nephrotoxicity remains unknown because of a lack of comparative studies.

In the present study, we evaluated whether 20 mEq of Mg supplementation was more effective than 8 mEq in preventing CDDP-induced nephrotoxicity. To our knowledge, this is the first report comparing the dose of Mg supplementation for the prevention of CDDP-induced nephrotoxicity. There was no significant difference in the incidence of CDDP-induced nephrotoxicity between the 8 mEq and 20 mEq groups. There was also no significant difference in the severity of nephrotoxicity, elevated SCr levels, and decreased estimated Clcr levels

between the two groups. Cardiac disease and albumin level, but not Mg dosage, were identified as independent risk factors for CDDP-induced nephrotoxicity.

The serum Mg store is estimated to account for only 0.3% of the total Mg in the entire body [25]; therefore, it is unclear whether serum Mg levels reflect total body Mg conditions, including the condition of the kidney. Saito et al. [24] reported that the renal protective effect of Mg supplementation could be observed as of the first course of chemotherapy, and the degree of serum Mg depletion remained constant in all subsequent cycles. These findings largely ruled out the mechanism underlying the protective effect of Mg against CDDP-induced nephrotoxicity involving the prevention of serum Mg depletion.

To assess the risk factors for CDDP-induced nephrotoxicity, we performed multivariate analyses. We found that cardiac disease and an albumin level ≤ 3.9 g/dL were associated with an increased risk for CDDP-induced nephrotoxicity. In general, CDDP-induced nephrotoxicity has been associated with reduced levels of plasma proteins that bind to CDDP. Approximately 98% of CDDP binds to plasma proteins such as albumin [26], and nephrotoxicity is associated with peak plasma CDDP levels and/or the area under the plasma CDDP concentration-time curve for unbound CDDP [27, 28]. It is well known that hypoalbuminemia can lead to elevated free platinum concentrations and enhanced nephrotoxicity. Several studies have also indicated an association between CDDP-induced nephrotoxicity and comorbidities such as cardiac disease [22, 23]. In patients with cardiac disease, a reduction in renal perfusion caused by decreased cardiac output may affect the clearance of drugs eliminated by renal excretion. For example, renal clearance of vancomycin is reduced in patients with heart disorders [29]. Thus, decreased renal perfusion associated with cardiac disease can influence the clearance of CDDP. In addition, regular use of non-steroidal anti-inflammatory drugs (NSAIDs), male sex, and poor PS have been reported as risk factors for CDDP-induced nephrotoxicity [15, 18]; however, these factors were not identified to increase the risk of CDDP-induced nephrotoxicity in this study. This is possibly due to the fact that nearly 80% of the patients in our cohort were male, with a majority PS score of 0 or 1. Male sex and poor PS were also not identified as independent risk factors in our previous study [20]. Regular use of NSAIDs could not be considered in this study because of the small number of included patients using NSAIDs. In the previous reports [13, 15–19, 24], forced diuresis was used to prevent CDDP-induced nephrotoxicity, as in this study, while hydration was supplied either through conventional methods or short hydration. The interrelationship between forced diuresis and type of hydration in the prevention of CDDP-induced nephrotoxicity is unknown. The optimal dosage of Mg supplementation under short hydration conditions is a subject for further investigation.

Under conditions of forced diuresis and conventional high-volume hydration, 20 mEq Mg supplementation had no greater preventive effect on CDDP-induced nephrotoxicity than 8 mEq. In Japan, magnesium sulfate products at 20 mEq are conventionally used as electrolyte supplements. Since magnesium sulfate preparations are not expensive, if the cost is acceptable, the use of 20 mEq as a packaging unit might be useful in terms of risk management against preparation errors.

This study has some limitations. First, this was a retrospective observational study and not a randomized or prospective study. Second, individual quantifiable data of heart disease (e.g., cardiac output and ejection fraction) were not available; therefore, we defined heart disorders based only on the medical history of cardiac diseases such as angina or myocardial infarction. Third, we were unable to examine other potential risk factors such as the regular use of NSAIDs. Fourth, the safety profile could not be determined in this pooled analysis

because adverse event data were not available in the medical records for this analysis. Fifth, the sample size was relatively small. Finally, the inclusion of only cases with both forced diuresis and conventional high-volume hydration, as a method for preventing nephrotoxicity other than Mg supplementation, limits the generalizability of the study results.

In conclusion, we did not find an advantage of 20 mEq Mg supplementation over 8 mEq in terms of a preventive effect against CDDP-induced nephrotoxicity. The optimal dose of Mg supplementation for the prevention of CDDP-induced nephrotoxicity remains unknown, and further studies, such as randomized clinical trials, are warranted. Careful monitoring of SCr levels during CDDP-based chemotherapy is recommended for patients with heart disease and hypoalbuminemia.

Declarations

Funding and/or conflicts of interest

The authors declare that they have no conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with Ethical Standards

Research Involving Human Participants

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committees, and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to participate and/or consent to publication

Not applicable; the requirement for informed consent was waived due to the retrospective nature of the study.

Availability of data and material

Data supporting the findings of this study are available from the corresponding author on reasonable request. However, restrictions apply to the availability of these data, which were used under a license for the current study and are thus not publicly available.

Code availability

Not applicable.

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Author contributions

TH and TM conceived of the study. TH performed statistical analyses. TM, TN and TE provided technical support. TM, TH, FO, KT, SM, and CY contributed to the interpretation of data and assisted in the preparation of the manuscript. TH and TM prepared the initial draft of the manuscript. TM, TH, FO, KT, SM, CY, TN and TE critically revised the manuscript. All authors reviewed and approved the final manuscript.

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Figures

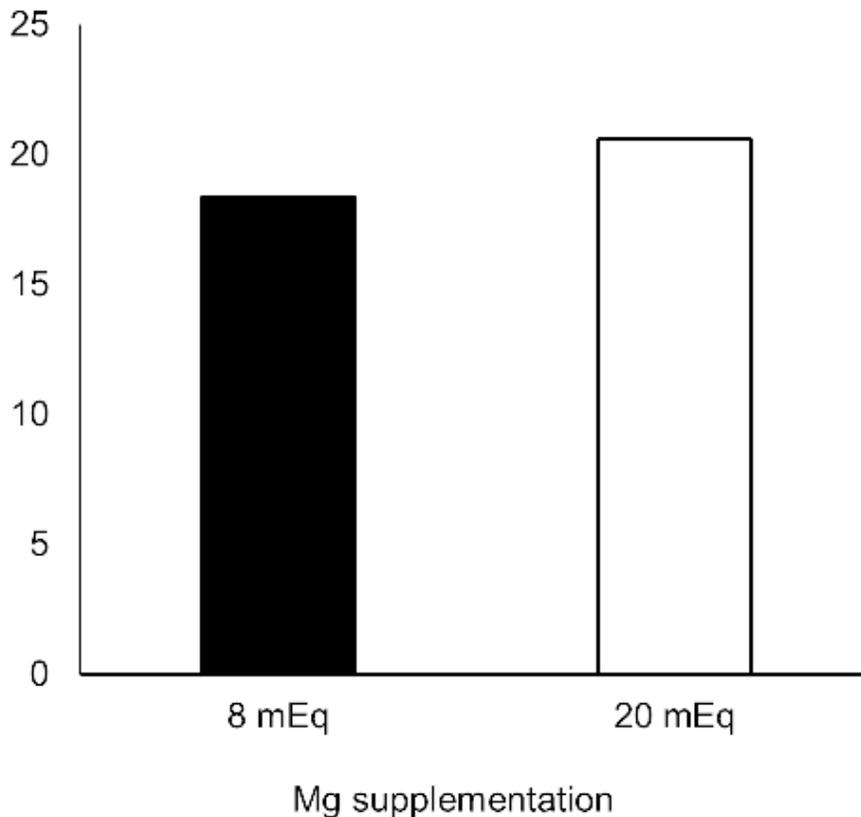


Figure 1

Incidence of nephrotoxicity according to Mg supplementation dose. The difference between the two groups was analyzed using the chi-square test

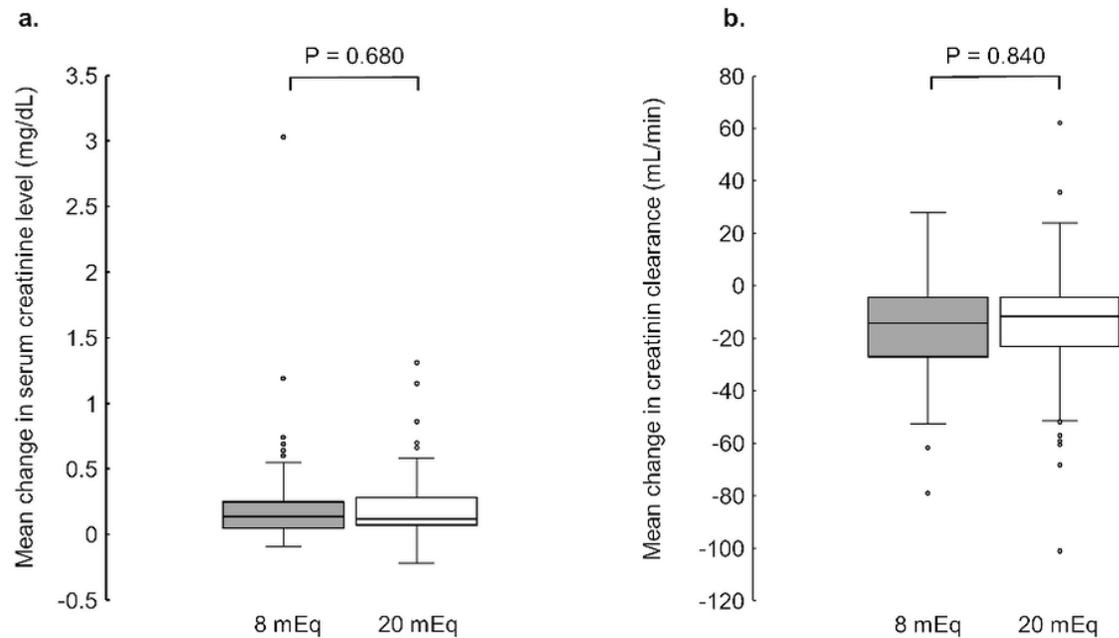


Figure 2

Comparison of Δ SCr and Δ CLcr between the 8 mEq and 20 mEq Mg supplementation groups in all subsequent cycles. Box-and-whisker plots for the relationship between 8 mEq and 20 mEq in the mean change of the (a) serum creatinine level (Δ SCr) and (b) creatinine clearance (Δ CLcr) during the subsequent cycles of CDDP-based chemotherapy. The difference between the two groups was analyzed using the unpaired Student t-test

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