Original Article

Effect of $MgSO_4$ Administration on The Incidence of Acute Kidney Injury and Renal Function in Lung Cancer Patients Receiving Cisplatin Chemotherapy

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Abstract

Background: Platinum-based chemotherapy is the most common lung cancer therapy currently performed with satisfactory results, but the use of platinum-based chemotherapy, such as cisplatin, can cause cisplatin-induced nephrotoxicity (CIN). $MgSO_4$ is a substance that has been studied and is known to have a protective effect on the kidneys. This study aims to determine the effect of $MgSO_4$ administration on the incidence of CIN in lung cancer chemotherapy patients receiving cisplatin chemotherapy.

Methods: This was a quasi-experimental study with a pre-test and post-test control group design. The study group received intravenous $MgSO_4$ 20 mEq, and the control group received standard therapy without $MgSO_4$. The incidence of CIN was assessed based on the incidence of acute kidney injury (AKI) and renal function measured by the estimated glomerulus filtration rate (eGFR).

Results: The incidence of AKI in the treatment group was 6.67%, whereas the control group had no incidence of AKI (*P*=0.32). Renal function (eGFR) showed no significant difference between the treatment and control groups (*P*=0.86), although both groups exhibited improved renal function post-chemotherapy.

Conclusion: $MgSO_4$ administration does not affect the incidence of AKI and renal function of lung cancer patients receiving cisplatin chemotherapy.

Keywords: AKI, cisplatin, lung cancer, $MgSO_4$, renal function

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Submitted: October 28th, 2024
Accepted: November 28th, 2025
Published: December 22nd, 2025

J Respirol Indones. 2025
Vol. 45 No. 4: 296-302
https://doi.org/10.36497/jri.v45i4.843

INTRODUCTION

Lung cancer is one of the most common types of cancer worldwide that arises from the uncontrolled growth of lung tissue cells.[1,2] There are more than 2 million cases of lung cancer every year.[3] Lung cancer accounts for 14.1% of all cancer cases in Indonesia and is the most commonly reported type of cancer in men.[4] There are two major classifications of lung cancer, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), which account for 85% of all lung cancer cases.[5]

Chemotherapy is the main option for lung cancer to date, with satisfactory therapeutic outcomes.[6] Platinum-based chemotherapy, such as cisplatin, is a common treatment for lung cancer, especially for patients with stage III or higher NSCLC who are ineligible for surgery.[7]

In Indonesia, cisplatin chemotherapy is the main therapy for lung cancer, both NSCLC and SCLC, which is covered by the national health insurance system.[4] However, the use of cisplatin can cause serious side effects such as nephrotoxicity, which can lead to worsening of the patient's condition, known as cisplatin-induced nephrotoxicity (CIN).[8] The incidence of CIN in lung cancer patients receiving cisplatin chemotherapy has been reported to be 6.51–10.06%.[9]

Various strategies have been developed to prevent CIN in lung cancer patients. One such strategy is $MgSO_4$ supplementation, which has been shown to protect the kidneys. Studies have shown that $MgSO_4$ can provide protective effects on both human and animal kidneys.[10] However, there are still a few studies that explain the impact of $MgSO_4$

supplementation on the incidence of CIN in lung cancer patients undergoing cisplatin chemotherapy.

Therefore, this study aims to determine the effect of $MgSO_4$ administration on the incidence of CIN in lung cancer patients, assessed by the incidence of acute kidney injury (AKI) and renal function.

METHODS

This was a quasi-experimental study with a pretest and post-test control group design. This study was conducted at dr. Moewardi General Hospital from March to May 2024. This study has been approved by the ethics committee (No 864/III/HREC/2024).

The inclusion criteria in this study were patients diagnosed with SCLC or NSCLC based on cytology or histology examination; never had history of chemotherapy; received chemotherapy by cisplatin in combination with taxan, pemetrexed or etoposide group; age 18–65 years old; has good renal function with estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2 and has 0 or 1 performance status based on ECOG. Meanwhile, the exclusion criteria include hypersensitivity to $MgSO_4$.

The CIN incidence was assessed by AKI incidence and renal function. The AKI incidence was defined as the increase in serum creatinine levels ≥0,3 mg/dL or an increase ≥1.5–2 fold from the baseline value. The incidence of AKI was assessed by comparing serum creatinine levels before and after the second cycle of chemotherapy. Creatinine evaluation was performed after the second cycle because nephrotoxicity typically develops within 10 days of cisplatin administration, peaking at 24–48 hours. The second cycle was chosen for evaluation because cumulative cisplatin doses increase the risk of nephrotoxicity, allowing for the assessment of kidney damage while the risk of patient dropout due to severe deterioration or mortality remained low. The renal function was measured by the eGFR value, that calculated based on the Cockcroft-Gault formula.

Patients who met the inclusion criteria were motivated to participate in the study and were informed about the procedures, risks, and objectives of the study. Patients were then asked to sign informed consent. Patients were then randomly divided into two groups into treatment and control groups. All patients were then examined for baseline anthropometric values and blood sampling for creatinine and eGFR levels, which were carried out before the first cycle of chemotherapy as baseline values for the assessment of renal function and before the second cycle of chemotherapy as baseline values for the assessment of the incidence of AKI.

Patients in the treatment group received standard therapy consisting of NaCl infusion, ondansetron IV 8 mg and furosemide IV 20 mg, accompanied by the administration of $MgSO_4$ at a dose of 20 mEq. The administration of $MgSO_4$ as much as 20 mEq uses 20% $MgSO_4$ preparation, which is given as much as 12.5 mL and dissolved in NaCl 0.9% 500 mL, which is then given to the patient within 2 hours. The control group only received standard therapy. $MgSO_4$ was given twice, once each before the first and second cycle of cisplatin administration. Administration of the first and second cycles of cisplatin, 3 weeks apart. Twenty-four hours after the completion of the second cycle of cisplatin chemotherapy, the patient was re-drawn blood for the measurement of creatinine levels for the assessment of the incidence of AKI and eGFR for the assessment of renal function.

Data are presented as mean±standard deviation for continuous data and n (%) for categorical data. All analysis will be conducted using IBM SPSS version 25. The value of $P<0.05$ is considered statistically significant.

RESULTS

There were 32 subjects in this study, 17 subjects in the treatment group and 15 subjects in the control group. No subjects dropped out of the control group. In the treatment group, two subjects were excluded: one due to severe hepatic impairment and one due to brain metastases requiring a change in therapeutic modality. The subject with hepatic impairment exhibited SGOT and SGPT elevations up

to five times the baseline value. Based on the results of data analysis, there were no significant differences in characteristics between the treatment and control groups. This indicates that the subjects in both groups tend to be homogeneous (Table 1).

Table 1. Subject's Characteristics

Variable	Treatment group (n=15)	Control group (n=15)	*P*
Sex			
Male	11 (73.33%)	12 (80.00%)	0.67
Female	4 (26.67%)	3 (20.00%)	
Age (years)			
20-30	1 (6.67%)	0 (0.00%)	
31-40	1 (6.67%)	1 (6.67%)	
41-50	2 (13.33%)	5 (33.33%)	0.72
51-60	6 (40.00%)	6 (40.00%)	
>60	5 (33.33%)	3 (20.00%)	
Body Mass Index			
Underweight	5 (33.33%)	8 (53.33%)	
Normoweight	9 (60.00%)	7 (46.67%)	0.48
Overweight	1 (6.67%)	0 (0.00%)	
Lung cancer type			
SCLC	0 (0.00%)	2 (13.33%)	0.14
NSCLC	15 (100.00%)	13 (86.67%)	
Lung cancer subtype			
SCC	6 (40.00%)	4 (26.67%)	
Adenocarcinoma	8 (53.33%)	9 (60.00%)	0.26
Neuroendocrine carcinoma	1 (6.67%)	0 (0.00%)	
SCLC	0 (0.00%)	2 (13.33%)	
Staging			
IVA	8 (53.33%)	10 (66.67%)	0.46
IVB	7 (46.67%)	5 (13.33%)	
Comorbidities			
No comorbidities	13 (86.67%)	13 (86.67%)	0.72
Hypertension	1 (6.67%)	2 (13.33%)	
CVD	1 (6.67%)	0 (0.00%)	
Chemotherapy combination regimen			
Docetaxel	2 (13.33%)	2 (13.33%)	
Paclitaxel	7 (46.67%)	7 (46.67%)	0.7
Pemetrexed	5 (33.33%)	4 (26.67%)	
Etoposide	1 (6.67%)	2 (13.33%)	
Drug history			
No drug history	13 (86.67%)	13 (86.67%)	
ACE-i	1 (6.67%)	0 (0.00%)	0.33
ARB	1 (6.67%)	2 (13.33%)	
NSAID	1 (6.67%)	0 (0.00%)	

Note: SCLC=Small cell lung carcinoma; NSCLC=Non-small cell lung carcinoma; SCC=Squamous cell carcinoma; CVD=Cardiovascular disease; ACE-i=Angiotensin converting enzyme inhibitor; ARB=Angiotensin receptor blocker; NSAID=Non-steroid anti-inflammatory drugs.

In the treatment group, one subject developed AKI after the second cycle of chemotherapy. Meanwhile, in the control group, there were no subjects who experienced AKI. The results of data analysis of differences in the incidence of AKI between the two groups obtained *P*=0.32. This indicates that there was no significant difference in the incidence of AKI between the two research groups (Table 2).

Table 2. AKI incidence between groups

AKI incidence	Treatment group (n=15)	Control group (n=15)	*P*
Yes	1 (6.67%)	0 (0.00%)	0.32
No	14 (93.33%)	15 (100.00%)	

Renal function assessed based on eGFR showed an increase in value in the treatment group, from 89.69 mL/min/1.73 m^2 to 92.14 mL/min/1.73 m^2, indicating an improvement in renal function. The same thing was observed in the control group, where an increase in value was also obtained from 88.94 mL/min/1.73 m^2 to 95.24 mL/min/1.73 m^2, indicating an improvement in renal function. However, the results of data analysis showed no significant difference in renal function 24 hours after the second cycle of chemotherapy between the treatment and control groups with *P*=0.86 (Table 3).

Table 3. Renal function between groups

Renal function	Treatment group (n=15)	Control group (n=15)	*P*
Baseline	89.69±23.14	88.94±19.54	0.92
24h post 2nd cycle chemotherapy	92.14±30.54	95.24±60.29	0.86

To further evaluate renal function, the change in eGFR values between groups was analyzed using an independent T-test (Table 4).

Table 4. Renal function changes between groups

Variable	Treatment group (n=15)	Control group (n=15)	*P*
Renal function changes	2.45±24.2	6.3±49.61	0.79

Several side effects were observed in the subjects of this study during the study period. Some of these side effects included anemia, nausea, diarrhea, peripheral neuropathy, neutropenia and worsening of liver function. There were 1 subject (6.67%) in the treatment group and 4 subjects (26.67%) in the control group who did not experience any side effects. The most prevalent side effect in the treatment group was nausea (33.33%), while in the control group was anemia (26.67%) (Table 5).

Table 5. Side effects of subjects

Side Effect	Treatment group (n = 15)	Control group (n = 15)
Anemia	2 (13.33%)	4 (26.67%)
Nausea	5 (33.33%)	2 (13.33%)
Diarrhea	2 (13.33%)	1 (6.67%)
Alopecia	2 (13.33%)	0 (0.00%)
Liver function worsening	0 (0.00%)	2 (13.33%)
Peripheral neuropathy	2 (13.33%)	1 (6.67%)
Neutrophenia	1 (6.67%)	1 (6.67%)

DISCUSSION

The results of this study indicate that the administration of $MgSO_4$ does not affect the incidence of AKI and renal function in lung cancer patients undergoing cisplatin chemotherapy. The incidence of AKI just found in just one subject given MgSO4. In addition, there was no difference in renal function between the group given $MgSO_4$ and controls. At 24 hours post-chemotherapy 2nd cycle, there was no significant difference in renal function, although there was an increase. This indicates that $MgSO_4$ has the same effectiveness as the control. At baseline, neither group suffered from AKI and had normal renal function, so the initial baseline characteristics of the two groups were relatively similar.

These results align with a study by Alizadeh-Hadadhania et al, which reported that magnesium administration had no impact on renal function and the incidence of CIN in cancer patients receiving platinum-based chemotherapy. This is thought to be due to the relatively short period of magnesium administration, which is for 2 weeks.[11] This is similar to research by Ashrafi et al in Iran, which reported that the administration of $MgSO_4$ 2 hours before cisplatin chemotherapy in patients with cancer showed no difference in renal function assessed based on serum creatinine levels compared to subjects who were only given hydration without $MgSO_4$. This is also thought to be due to the small number of samples, so that it cannot see a broader picture of the effect of $MgSO_4$ on renal function.[12]

Different results were shown by the study of Hase et al in Japan, which reported that giving short hydration accompanied by magnesium at a dose of 20 mEq in patients with lung cancer who received cisplatin chemotherapy with an average cisplatin dose of 80 mg/m^2 could have a protective effect on the kidneys. In contrast to this study, which used a cisplatin dose of ≥60 mg/m^2, the study used a higher cisplatin dose with an average of 80 mg/m^2. In addition, the mean baseline eGFR in that study was lower at 82.3 mL/min/1.73 m^2 compared to this study, which was 89.69 mL/min/1.73 m^2.[13] The use of higher doses of cisplatin in previous studies compared to this study is likely to cause nephrotoxicity, so that the protective effect of magnesium can be seen.

Cisplatin is an antineoplastic agent that has been widely used in various types of cancer with satisfactory therapeutic results. Some types of cancer that often use cisplatin include head and neck cancer, lung cancer, testicular cancer, melanoma, breast cancer and lymphoma.[14] Cisplatin can be concentrated in high levels in the kidneys and can reach higher concentrations in the blood of patients undergoing chemotherapy.[15]

Cisplatin is excreted from the blood into the kidneys. Cisplatin, which is concentrated in the kidneys, will then be reabsorbed into the renal tubular cells through the transport proteins OCT2, CTR1, and OAT1/3.[15] Cisplatin that has been reabsorbed will then form a highly reactive thiol, which is a compound with nephrotoxicity. This compound will then be effluxed with the help of MATE1 and MATE2 transport proteins to the lumen of the renal tubules and excreted along with urine. Incomplete excretion leads to cisplatin retention, causing damage to renal tubular cells.[16,17]

Cisplatin can also cause electrolyte imbalance, such as hypomagnesemia.[18] Hypomagnesemia can further aggravate the CIN because it can disrupt the regulation of OCT2 and MATE1 transport proteins in renal tubular cells. Thus, this will make the accumulation of cisplatin higher in the renal tubules and result in further damage, such as the occurrence of AKI.[19]

Administration of cisplatin results in a decrease in renal function in the first 6 hours after administration and peaks at 72 hours after administration.[20,21] In this study, serum creatinine was assessed 24 hours after the second chemotherapy cycle; consequently, delayed changes in renal function or AKI onset may have been missed,

potentially explaining the lack of observed differences between the groups.[22]

Another reason that may also explain this finding is the good renal function of the subjects, because the subjects in this study were predominantly in the 51–60 years age group. Renal function declines significantly when age reaches 65–70 years.[22] This is as reported by Duan et al, which stated that the incidence of CIN in elderly patients was higher than in young patients.[9]

Another possibility is that the magnesium levels in the patient's blood may be sufficient to provide a protective effect on the kidneys. Some foods commonly consumed by Indonesians, such as rice and tofu, are known to be rich in magnesium.[23] This could have an impact on the difference in the incidence of AKI in Indonesian patients and other countries.

A study by Rachman et al in Indonesia reported an AKI incidence rate of 10.4% in patients who received NaCl hydration before undergoing cisplatin chemotherapy.[24] This is relatively lower than in other countries. A study by Dierckes et al in the United States reported an incidence of AKI of 54.5% after chemotherapy with cisplatin.[25] This highlights the need for further research, given the limited data on cisplatin-induced AKI in Indonesia. Some other foods commonly consumed by Indonesians that are high in magnesium include fish and vegetables such as spinach and moringa.[26–28]

The prevalence of hypomagnesemia in cancer patients receiving cisplatin chemotherapy also varies from 40% to 90%. In addition to the CIN, other factors contribute to the incidence of hypomagnesemia, including inadequate magnesium intake, diarrhea, and vomiting.[29] In individuals with normal magnesium levels, there is a reduced risk of cisplatin-induced AKI.[30,31]

The administration of cisplatin as chemotherapy is generally given at high doses, increasing the possibility of various side effects such as neurotoxicity, ototoxicity and nephrotoxicity. A common procedure to reduce the side effects of cisplatin, especially nephrotoxicity, is aggressive hydration using NaCl fluid.[32] Hydration can reduce the half-life, the transit time in the renal tubules and the concentration of cisplatin in the urine.[33,34]

Inadequate nutrition and hydration status before chemotherapy with cisplatin may increase the risk of nephrotoxicity. The protective mechanism of hydration is thought to be due to volume expansion, resulting in increased renal excretion of cisplatin. Administration of electrolytes such as NaCl also has a protective effect against cisplatin by preventing a decrease in osmolality and thus preventing the osmotic stress response.[33,34]

In this study, subjects received hydration with NaCl both as routine fluid therapy and as fluid therapy given together with cisplatin. Additionally, oral fluid intake was not controlled. Thus, subjects' baseline hydration may have been adequate to provide a protective effect against cisplatin-induced nephrotoxicity.

LIMITATION

In this study, chemotherapy was administered for only two cycles rather than the standard four to six, which may not have fully captured potential nephrotoxic effects; this represents a limitation of the current analysis. Furthermore, the abbreviated treatment duration precluded the assessment of longitudinal trends in renal function.

CONCLUSION

The results indicate that $MgSO_4$ administration did not significantly affect the incidence of AKI or renal function in lung cancer patients receiving cisplatin chemotherapy.

ACKNOWLEDGMENTS

We thank the staff of the Department of Pulmonology and Respiratory Medicine and the Department of Internal Medicine, Faculty of Medicine, Universitas Sebelas Maret and dr. Moewardi General Hospital, Surakarta, Indonesia.

CONFLICT OF INTEREST

The authors declare no conflicts of interest regarding this study.

FUNDING

This research did not receive funding from any individual or institution.

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