석 사 학 위 논 문

Determinants of Acute Kidney Injury Following Mannitol Administration in Neurocritically Ill Patients: An Based on Pre-Therapy Data

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이 논문을 석사학위 논문으로 제출함

2024년 8월

계 명 대 학 교 대 학 원

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특히 홍정호 지도교수님께서는 연구 방향 설정, 데이터 분석 및 논문 작성에 이르기까지 지속적으로 세심한 지도를 해주셨습니다. 교수님의 풍부한 지식과 경험은 제 연구의 큰 길잡이가 되었으며, 교수님의 격려와 조언 덕분에 어려운 순간들도 극복할 수 있었습니다.

또한 연구의 진행을 위해 노고해주신 모든 분들께도 진심으로 감사드립니다. 특히, 연구실에서의 협조와 동료들의 지원은 큰 힘이 되었습니다. 이러한 도움과 지원이 없었다면 이 연구를 이루어내기 어려웠을 것입니다.

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1. Introduction

Mannitol is widely used for the treatment of brain edema or increased intracranial pressure after a traumatic brain injury, ischemic stroke, or hemorrhagic stroke (1). However, high doses or prolonged use of mannitol can lead to adverse effects such as acute kidney injury (AKI), electrolyte imbalance, hypotension, and rebound elevated intracranial pressure.

Previous studies have demonstrated the risk factors associated with AKI observed during mannitol infusion in neurocritical care patients, and its impact on mortality in these patients (2). Although the incidence and risk factors of mannitol-associated AKI in acute stroke patients have been investigated (3), the precise relationship between mannitol administration and kidney injury in neurocritical care patients, and the risk factors contributing to AKI based on data prior to mannitol administration are not evaluated (1).

Severe AKI, defined as stage 2 and stage 3 according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, represents a critical subset of AKI associated with higher morbidity and mortality rates (4). This severity classification highlights the importance of early detection and intervention. Assessing severe AKI is essential for identifying serious renal complications, thereby enabling better risk stratification and providing effective interventions (5).

The aim of this study is to evaluate independent factors that increase the risk of severe AKI prior to mannitol administration in neurocritical care patients. Assessing these risk factors can enable us to develop targeted prevention strategies to reduce AKI incidence, improve clinical decision-making, and optimize patient management. Ultimately, the

findings might improve the clinical guidelines and protocols, leading to better care for neurocritically ill patients undergoing mannitol therapy.

2. Materials and Methods

2.1. Study population:

This was a retrospective, single-center, observational study including patients aged ≥18 years, admitted to the Department of Neurology and Neurosurgery at Keimyung University Dongsan Hospital between August 2018 and June 2021, received mannitol for the treatment of brain edema and elevated intracranial pressure. The inclusion criteria for this study were patients who received mannitol at least once during their hospital stay. Patients were excluded if they had a history of hemodialysis, peritoneal dialysis, or renal transplantation, if laboratory data for blood urea nitrogen (BUN), serum creatinine, and estimated glomerular filtration rate (eGFR) values prior to the initial administration of mannitol were not available.

This study was approved by the institutional review board (IRB) of Dongsan Hospital (IRB number 2024-04-011). Patient records were reviewed and analyzed according to the Declaration of Helsinki.

2.2. Data collection and definitions of AKI:

In this study, demographics, diagnoses, clinical characteristics, past medical histories, and laboratory findings were collected retrospectively using Clinical Data Warehouse. We collected data on age, sex, body weight, height, and the primary diagnosis at admission such as ischemic stroke, hemorrhagic stroke, traumatic brain injury or other conditions

(central nervous system tumor, central nervous system infection, status epilepticus etc.). Medical history of hypertension, diabetes mellitus, chronic kidney disease (CKD), liver cirrhosis, and chronic heart failure was also documented. Information on medical history was collected from electronic medical records, database nursing information sheets, and present illness forms. CKD was defined according to the KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of initial eGFR after admission in neurocritically ill patients (6). We also recorded systolic blood pressure (SBP), diastolic blood pressure (DBP), SpO2, pulse rate, respiratory rate, and body temperature.

Patients' level of consciousness was classified into three groups based on the total Glasgow Coma Scale (GCS) score: GCS 3-8, GCS 9-12, and GCS 13-15 (7). Laboratory data on osmolality, AST, ALT, hemoglobin, albumin, platelet, eGFR Chronic Kidney Disease Epidemiology Collaboration (eGFR CKD-EPI), serum creatinine, glucose, BUN, serum chloride, serum sodium, serum potassium levels prior to the initial mannitol administration were collected. Given that CT and MRI contrasts administered within 72 hours can affect the risk of contrast-induced AKI, we assessed the administration of contrast agents within 72 hours prior to the initial administration of mannitol (8, 9).

We followed the diagnostic criteria for AKI outlined in the 2012 edition of the KDIGO Clinical Practice Guidelines (10). Baseline serum creatinine was defined as creatinine levels before the first administration of mannitol after hospitalization. AKI stage 1 was defined as an increase in serum creatinine by 1.5 to 1.9 times within 7 days or an increase of at least 0.3 mg/dL within 24 hours; stage 2 was defined as an increase in serum creatinine by 2.0 to 2.9 times within 7 days; stage 3 was defined as an increase in serum creatinine by 3.0 times within 7 days or an increase to $\geq$4.0 mg/dL within 24 hours. Patients who received renal

replacement therapy after hospitalization were also classified as stage 3 AKI. Non-severe AKI was classified as stage 0 and stage 1 based on the KDIGO classification, and severe AKI was classified as stage 2 and stage 3 (3, 4).

2.3. Statistical analysis:

Categorical variables were compared using the chi-square test and continuous variables were compared using t-test. Fisher's exact test and the Mann-Whitney U test were used for variables with non-normal distribution. Categorical and continuous variables were expressed as frequency (%) and median (interquartile range, IQR), respectively. Multivariate logistic regression analyses were conducted using variables that were statistically significantly different between non-severe AKI and severe AKI in a bivariate analysis (p values < 0.05) was used to identify significant determinants for severe AKI occurrence and odds ratios (OR) with 95% confidence interval (CI) were calculated. Variables with substantial collinearity (determined as variance inflation factor ≥ 10) were excluded from the multivariate logistic regression analysis.

All analyses were performed using R statistical software (version 4.3.2). P values < 0.05 were considered statistically significant.

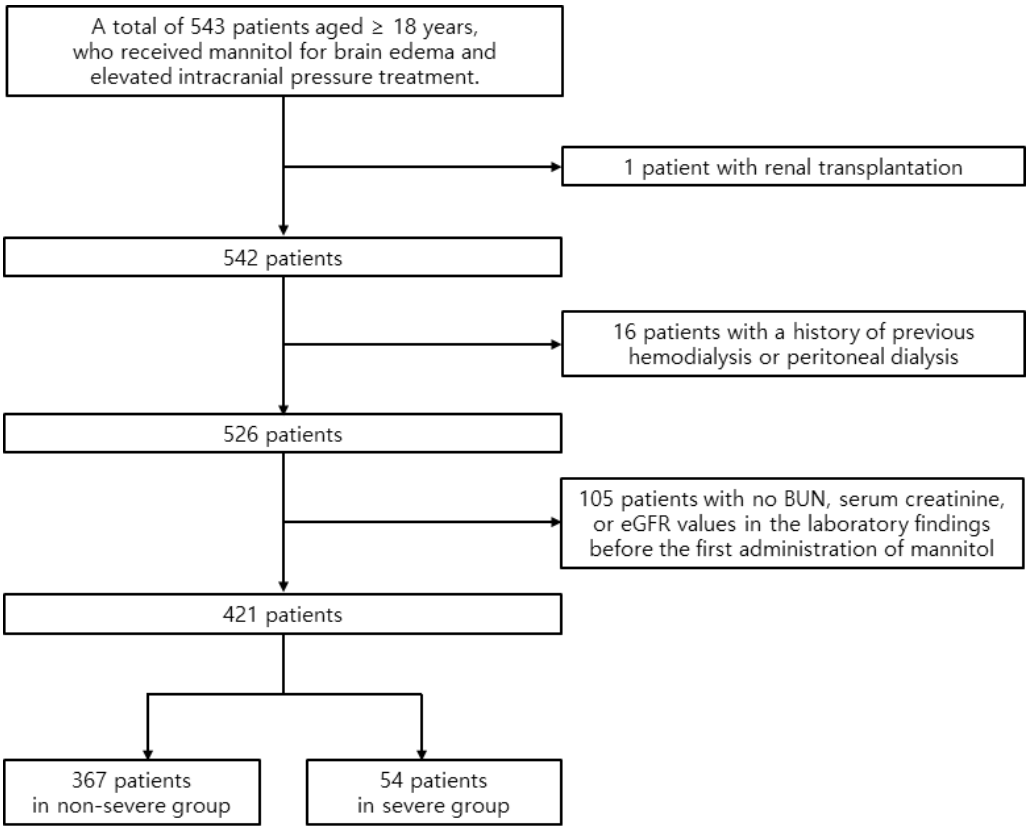

Figure 1. Patients inclusion flowchart.

3. Results

3.1. Baseline characteristics:

During the study period, 543 patients were reviewed retrospectively and 122 patients were excluded. Excluded patients comprised of 16 patients with a history of hemodialysis or peritoneal dialysis, 1 with renal transplantation, and 105 did not have laboratory data on BUN, serum creatinine, or eGFR values before the first administration of mannitol. A total of 421 patients were included in the analysis, of whom 367 (87.2%) were classified as non-severe AKI group and 54 (12.8%) as the severe AKI group (Figure 1, Table 1). The median age was 64.0 [53.0;75.0] years and 50.6% of the patients were male.

No significant differences were observed in sex, height, or body weight between the non-severe and severe groups. Age showed a significant difference (63.0 [53.0;73.0] vs. 70.0 [54.0;79.0], $p < 0.05$). The prevalence of ischemic stroke was notably higher in the severe group compared to the non-severe group (29.6% vs. 9.5%, $p < 0.001$). No significant differences were found in rates of hemorrhagic stroke, traumatic brain injury, or other diagnoses. The number of patients with chronic kidney disease was significantly higher in the severe group compared to the non-severe group (94.4% vs. 22.9%, $p < 0.001$). There were no significant differences in the prevalence of hypertension, diabetes mellitus, liver cirrhosis, or chronic heart failure.

For the clinical characteristics measured before mannitol administration, pulse rate was found to be statistically significantly higher in the severe AKI group (81.0 [72.0;91.0] vs. 87.0 [78.0;99.0], $p < 0.05$). The proportion

of levels of consciousness as measured by the GCS was significantly different between the two groups (non-severe group vs severe group; 18.3% vs. 63.0% for GCS 3-8, 24.5% vs 18.5 for GCS 9-12, 57.2% vs 18.5% for GCS 13-15, $p < 0.001$). However, there were no significant differences in SBP, DBP, SpO2, respiratory rate, and body temperature between the groups. The use of CT contrast agents within 72 hours (55.3% vs. 77.8%, $p < 0.05$) and the initial mannitol dose (0.5 [0.4;0.6] vs. 0.7 [0.5;0.9], $p < 0.001$) also showed significant differences. No significant differences were observed in the use of MRI contrast agents within 72 hours, beta-blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), calcium channel blockers, diuretics, or non-steroidal anti-inflammatory drugs (NSAIDs).

In the laboratory data measured before mannitol administration, significant differences were observed between the two groups for A ST (26.0 [20.0;35.0] vs. 31.5 [22.0;48.0], $p < 0.05$), albumin (4.4 [4.0;4.6] vs. 4.0 [3.7;4.5], $p < 0.05$), eGFR CKD-EPI (91.9 [81.1;103.0] vs. 81.5 [58.1;96.5], $p < 0.05$), serum creatinine (0.7 [0.6;0.9] vs. 0.8 [0.7;1.2], $p < 0.05$), glucose (139.0 [116.0;166.0] vs. 147.5 [121.0;183.0], $p < 0.05$), serum chloride (103.0 [100.0;105.0] vs. 101.5 [98.0;104.0], $p < 0.05$), and serum sodium (139.0 [137.0;141.0] vs. 139.0 [136.0;140.0], $p < 0.05$). No significant differences were observed between the two groups for serum osmolality, ALT, hemoglobin, platelet count, BUN, and serum potassium level (Table 2).

3.2. Predictors of AKI occurrence:

In multivariate logistic regression analysis, the following factors were

included to be independently significant: age in demographic information, ischemic stroke in primary diagnosis, CKD in medical histories, pulse rate and GCS in clinical characteristics, initial mannitol dose (g/kg) and use of CT contrast agents within 72 hours, beta-blockers in treatment, and AST, albumin, eGFR CKD-EPI, serum creatinine, glucose, serum chloride, and serum sodium in laboratory findings.

However, SBP, DBP, SpO2, respiratory rate, body temperature, use of MRI contrast agents within 72 hours, ACEI/ARB, calcium channel blockers, diuretics, NSAIDs, serum osmolality, ALT, hemoglobin, platelet, BUN, and serum potassium were no significant differences in the multivariate logistic regression analysis (Table 3).

3.3. Clinical outcomes:

After adjusting for confounders, ischemic stroke in primary diagnosis (OR 2.63, 95% CI [1.02, 6.86], $p < 0.05$), history of CKD in past medical histories (OR 79.3, 95% CI [22.8, 392], $p < 0.001$), a GCS score of 3 to 8 (OR 4.57, 95% CI [1.62, 13.9], $p < 0.01$), use of CT contrast agents within 72 hours (OR 2.83, 95% CI [1.12, 7.69], $p < 0.05$), AST (OR 0.99, 95% CI [0.99, 1.00], $p < 0.05$) remained independent predictors for the occurrence of severe AKI. Figure 2 shows the variables found to be significant in the logistic regression model.

Table 1. Patients with varying AKI Stages in Non-severe and Severe AKI Groups

Stage of AKI	Non-severe AKI (N=367)	Severe AKI (N=54)
AKI stage 0	37 (10.1%)	-
AKI stage 1	330 (89.9%)	-
AKI stage 2	-	26 (48.1%)
AKI stage 3	-	28 (51.9%)

AKI: acute kidney injury.

Table 2A. Comparison between Non-Severe AKI Group and Severe AKI Group (continued)

Variables	Non-Severe AKI (N=367, 87.2%)	Severe AKI (N=54, 12.8%)	p value
Demographic information			
Age, years	63.0 [53.0;73.0]	70.0 [54.0;79.0]	< 0.05**
Sex, male	185 (50.4)	28 (51.9)	NS
Height, cm	163.0 [156.0;170.0]	162.0 [157.0;170.0]	NS
Body Weight, kg	60.0 [53.5;70.0]	62.5 [53.0;70.0]	NS
Diagnosis, n (%)			
Ischemic stroke	35 (9.5)	16 (29.6)	< 0.001***
Hemorrhagic stroke	222 (60.5)	31 (57.4)	NS
Traumatic brain injury	34 (9.3)	2 (3.7)	NS
Others§	72 (19.6)	5 (9.3)	NS
Past medical histories, n (%)			
Hypertension	181 (49.3)	29 (53.7)	NS
Diabetes mellitus	85 (23.2)	16 (29.6)	NS
CKD	84 (22.9)	51 (94.4)	< 0.001***
Liver cirrhosis	4 (1.1)	1 (1.9)	NS
Chronic heart failure	13 (3.5)	4 (7.4)	NS

Table 2B. Comparison between Non-Severe AKI Group and Severe AKI Group (continued)

Variables	Non-Severe AKI (N=367, 87.2%)	Severe AKI (N=54, 12.8%)	p value
Clinical characteristics			
SBP, mmHg	139.0 [127.0;151.0]	139.0 [126.0;146.0]	NS
DBP, mmHg	82.0 [75.0;90.0]	77.0 [71.0;89.0]	NS
SpO_2, %	98.0 [97.0;99.0]	98.0 [97.0;99.0]	NS
Pulse Rate, bpm	81.0 [72.0;91.0]	87.0 [78.0;99.0]	< 0.01**
Respiratory Rate, bpm	20.0 [19.0;20.0]	20.0 [19.0;20.0]	NS
Body temperature, °C	36.7 [36.5;37.0]	36.8 [36.3;37.2]	NS
Glasgow Coma Scale			< 0.001**
13-15	210 (57.2)	10 (18.5)	
9-12	90 (24.5)	10 (18.5)	
3-8	67 (18.3)	34 (63.0)	
Treatment			
Initial mannitol dose, g/kg	0.5 [0.4; 0.6]	0.7 [0.5; 0.9]	< 0.001**
Use of CT contrast agents within 72 hours, %	203 (55.3)	42 (77.8)	< 0.01**
Use of MRI contrast agents within 72 hours, %	26 (7.1)	1 (1.9)	NS
Beta blocker, %	53 (14.4)	15 (27.8)	< 0.05*
ACEI/ARB, %	89 (24.3)	12 (22.2)	NS
Calcium channel blocker, %	146 (39.8)	22 (40.7)	NS
Diuretics, %	61 (16.6)	15 (2.8)	NS
NSAIDs, %	220 (59.9)	33 (61.1)	NS

Table 2C. Comparison between Non-Severe AKI Group and Severe AKI Group

Variables	Non-severe AKI (N=367, 87.2%)	Severe AKI (N=54, 12.8%)	p value
Laboratory findings			
Serum osmolality, mOsm	290.0 [285.5;295.0]	292.5 [284.0;302.0]	NS
AST, U/L	26.0 [20.0;35.0]	31.5 [22.0;48.0]	< 0.05*
ALT, U/L	19.0 [13.5;28.0]	23.0 [13.0;35.0]	NS
Hemoglobin, g/dL	13.1 [11.9;14.4]	12.4 [11.1;14.6]	NS
Albumin, g/dL	4.4 [4.0; 4.6]	4.0 [3.7; 4.5]	< 0.01**
Platelet, 10^3/μL	229.0 [184.0;276.5]	212.5 [158.0;252.0]	NS
eGFR CKD-EPI (average pre-mannitol), ml/min/1.73 m^2	91.9 [81.1;103.0]	81.5 [58.1;96.5]	< 0.01**
eGFR CKD-EPI (pre-mannitol), ml/min/1.73 m^2	92.5 [80.7;104.3]	81.2 [52.2;96.5]	< 0.001***
Initial eGFR CKD-EPI, ml/min/1.73 m^2	90.9 [80.1;102.5]	80.3 [60.1;95.6]	< 0.01**
Serum creatinine, mg/dL	0.7 [0.6; 0.9]	0.8 [0.7; 1.2]	< 0.01**
Glucose, mg/dL	139.0 [116.0;166.0]	147.5 [121.0;183.0]	< 0.05*
BUN, mg/dL	15.0 [12.0;19.0]	16.0 [12.0;24.0]	NS
Serum chloride, mEq/l	103.0 [100.0;105.0]	101.5 [98.0;104.0]	< 0.05*
Serum potassium, mEq/l	4.0 [3.7; 4.3]	4.1 [3.6; 4.5]	NS
Serum sodium, mEq/l	139.0 [137.0;141.0]	139.0 [136.0;140.0]	< 0.05*

ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ALT: alanine transaminase; AST: aspartate transaminase; BUN: blood urea nitrogen; CKD: chronic kidney disease; DBP: diastolic blood pressure; eGFR CKD-EPI; estimated Glomerular Filtration Rate Chronic Kidney Disease Epidemiology Collaboration; IQR: interquartile range; NSAIDs: nonsteroidal anti-inflammatory drugs; NS: non-significant SBP: systolic blood pressure; SD:

standard deviation; SpO_2: Peripheral capillary oxygen saturation; Continuous variables are expressed as the median (IQR) or as the mean ± SD. Categorial variables are expressed as counts (%); *: $p < 0.05$; **: $p < 0.01$; ***: $p <$ 000.1; §: Patients with primary diagnoses that do not include ischemic stroke, hemorrhagic stroke, or traumatic brain injury, such as CNS tumor, CNS infection, status epilepticus, etc.

Table 3. Multivariate Logistic Regression Analysis

	Multivariable analysis		
	OR	95% CI	p value
Age, years	0.99	[0.96, 1.02]	NS
Ischemic Stroke	2.63	[1.02, 6.86]	< 0.05*
CKD	79.3	[22.8, 392]	< 0.001***
Glasgow Coma Scale			
13-15			reference
9-12	1.26	[0.41, 3.87]	NS
3-8	4.57	[1.62, 13.9]	< 0.01**
Initial mannitol dose, g/kg	0.46	[0.12, 1.61]	NS
Use of CT contrast agents within 72 hours	2.83	[1.12, 7.69]	< 0.05*
Beta-blocker, %	1.32	[0.53, 3.20]	NS
Pulse Rate, bpm	0.98	[0.96, 1.01]	NS
AST, U/L	0.99	[0.99, 1.00]	< 0.05*
Albumin, g/dL	0.63	[0.29, 1.34]	NS
eGFR CKD-EPI (pre-mannitol), ml/min/1.73 m^2	1.02	[0.99, 1.04]	NS
Serum creatinine, mg/dL	1.10	[0.57, 2.12]	NS
Glucose, mg/dL	1.00	[1.00, 1.01]	NS
Serum chloride, mEq/l	0.88	[0.77, 1.00]	NS
Serum sodium, mEq/l	0.97	[0.84, 1.13]	NS

AST: aspartate transaminase; CI: confidence interval; CKD: chronic kidney disease; eGFR CKD-EPI; estimated Glomerular Filtration Rate Chronic Kidney Disease Epidemiology Collaboration; OR; odds ratio; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 000.1$.

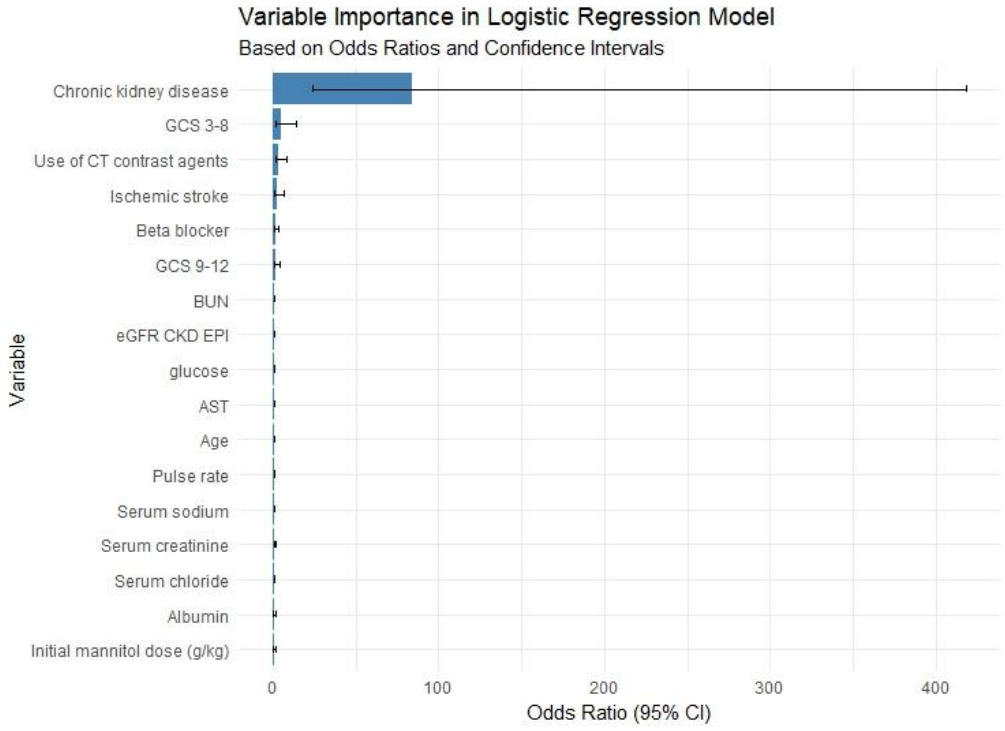

Figure 2. Variable importance in logistic regression model based on odds ratios and confidence intervals.

4. Discussion

In this study we categorized neurocritically ill patients into non-severe and severe AKI groups to evaluate the predictors for severe AKI occurrence based on patients' clinical and laboratory variables before mannitol administration. Severe AKI is a critical condition of deterioration in kidney function leading to increased mortality and prolonged hospital stays. Evaluating the risk factors for severe AKI is essential for early identification and management to prevent progression in these patients and to optimize patient outcomes.

Our study found that the incidence of severe AKI was 12.8%, which was similar to an incidence rate of 10.5% reported in a previous study (3). However, some studies have reported different incidence rates due to differences in the definition of severe AKI used in those studies (11). For this study, we defined severe AKI as stage 2 and stage 3 similar to the criteria used by Fiorentino et al. (12). In contrast, another study used the definition of stage 3 only as the selecting criterion for severe AKI, which possibly explains the difference in observed incidence rates (13). Our study aimed to provide a more granular evaluation of severe AKI by including patients with both stage 2 and stage 3 AKI, as defined by the KDIGO criteria.

In this study, we identified ischemic stroke, a history of CKD, a GCS score of 3 to 8, use of CT contrast agents within 72 hours, and AST levels as risk factors for severe AKI prior to mannitol administration. In this study data were collected from admission to just before mannitol administration, unlike most previous studies that analyzed AKI risk using data obtained during mannitol use (2, 14). Our findings suggest that observing these clinical factors before starting mannitol indicates a

potential for severe AKI, thus warranting caution. Other studies focused on data changes during mannitol use because of which the findings presented in those studies differed to the current one, such as variations in the osmolar gap. These differences stem from varying study objectives and methodologies.

In previous studies, severity in stroke patients was evaluated using initial National Institutes of Health Stroke Scale (NIHSS), which has been identified as a risk factor for AKI (2, 14). However, our study targeted neurocritically ill patients including those with traumatic brain injury, central nervous system tumors, central nervous system infections, status epilepticus, and a range of other neurocritical conditions, along with stroke patients. Further, we used GCS score, which provides a global rating of patient's level of consciousness and is broadly applicable across various conditions to assess the severity of our subjects (15).

The severity of brain injury can impact kidney function through dysfunction of autoregulation in brain and kidney (16). Additionally, brain injury-induced sympathetic activation, inflammation, and immune responses result in blood-brain barrier disruption leading to systemic inflammation, which exacerbates renal injury. Elevated AST level often reflects systemic inflammation and oxidative stress, increasing vascular permeability and endothelial damage in the kidneys (12, 16, 17). This systemic response likely contributes to our finding that a GCS score of $\leq$ 8 is a risk factor for AKI. By assessing the severity of neurological conditions through measures like the GCS score, we can better understand and manage the interplay between brain injury and kidney function in neurocritically ill patients.

Moreover, a previous study demonstrated that CKD was associated with AKI in neurocritically ill patients (2). Similarly, our study showed that a history of CKD was a significant risk factor for AKI before

mannitol infusion in neurocritically ill patients. CKD patients have reduced renal reserve, making them more susceptible to added insults from mannitol. Additionally, CKD is associated with chronic inflammation, oxidative stress, and endothelial dysfunction which can exacerbate renal injury when exposed to the osmotic effects of mannitol. As a result, a history of CKD significantly increases the probability of developing AKI (18).

In our study, we showed that the use of CT contrast agents within 72 hours before mannitol administration was a significant risk factor for severe AKI. According to Myung et al. (19), the use of CT contrasts 48-72 hours prior increases the likelihood of contrast-induced AKI. CT contrast agents can cause nephrotoxicity through direct tubular toxicity and renal ischemia induced by vasoconstriction and oxidative stress. Thus, this mechanism highlights the importance of monitoring CT contrasts use prior to mannitol administration (20).

Our study did not use data collected after mannitol administration, hence, we could not assess such variables as risk factors for AKI (factors such as osmolar gap, measured osmolality, and the measurement of mannitol dosage, or hourly urine output (ml/min)) which have been identified in other studies. Previous studies focused on AKI determinants following mannitol administration, which differs from the purpose of our study (2, 14, 21). Additionally, we examined the use of antihypertensive medications such as beta-blockers, ACEI/ARB, calcium channel blockers, diuretics, and NSAIDs before mannitol administration. Diuretics and other antihypertensive medications can increase the likelihood of AKI (14). A previous study confirmed the concurrent use of diuretics during mannitol administration. Mannitol induces significant reductions in water and sodium reabsorption along the entire nephron. When mannitol is used concurrently with diuretics it can cause profound diuresis, volume

depletion, and increase severity of AKI (22, 23). Since our study assessed medication use before mannitol administration, diuretics were not identified as an independent risk factor for severe AKI.

Despite the wealth of meaningful data, current study has some limitations. First, our study is of a non-randomized retrospective design and was conducted at a single center. Hence, the data should be interpreted cautiously. Second, accurate assessment of the volume status of patients before mannitol administration is crucial for understanding the development of AKI post-mannitol use. However, we could not precisely determine the volume status of patients prior to mannitol administration. Typically, patients' fluid balance which is indicative of hydration and kidney function is monitored. Third, the definition of CKD (according to the KDIGO guidelines) requires evaluating changes in eGFR over three months. Since this study was retrospective in design, we could not identify and evaluate laboratory changes that occurred in the three months prior to hospitalization. Therefore, we assessed CKD based on initial eGFR after admission and based on presence of history of hypertension and diabetes mellitus.

In conclusion, our study identified several independent risk factors of severe AKI in neurocritically ill patients who were treated with mannitol. Patients with ischemic stroke, history of CKD, severe impairment of consciousness, on whom CT contrast agents were used within 72 hours before mannitol administration, and had elevated AST level were at increased risk of developing severe AKI. These findings highlight the importance of careful assessment and monitoring of these factors before administering mannitol to neurocritically ill patients. Early identification of patients with these risk factors can help in implementing preventative measures and developing more effective treatment strategies to minimize the occurrence of AKI.

5. Summary

Herein, we have investigated pre-administration risk factors for acute kidney injury (AKI) in 421 neurocritically ill patients receiving mannitol. Severe AKI defined as stage 2 and 3 by KDIGO criteria was observed in 54 patients (12.8%).

This analysis revealed multiple factors that significantly contributed to the risk of severe AKI. Key predictors included ischemic stroke, history of CKD, pronounced consciousness impairment, recent use of CT contrast agents within 72 hours before mannitol administration, and elevated AST level.

These findings highlighted the importance of thorough pre-administration assessments including evaluation of kidney function, consciousness level, and recent use of contrast agents. Early identification of these risk factors can help implement preventative measures and develop more effective treatment strategies to reduce the incidence of severe AKI.

These findings necessitate increased vigilance and personalized management strategies for at-risk patients prior to mannitol treatment.

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Determinants of Acute Kidney Injury Following Mannitol Administration in Neurocritically Ill Patients: An Analysis Based on Pre-Therapy Data

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(Abstract)

Mannitol is widely used for the treatment of brain edema or increased intracranial pressure following traumatic brain injury, ischemic stroke, and hemorrhagic stroke. However, high doses or prolonged use of mannitol can cause acute kidney injury (AKI). This study aimed to evaluate independent factors that increase the risk of severe AKI prior to mannitol administration. We conducted a retrospective analysis of 421 patients who received mannitol at Keimyung University Dongsan Hospital between August 2018 to June 2021. Among them, 367 had non-severe AKI and 54 had severe AKI. The variables that were significantly different between the non-severe and the severe group included age, ischemic stroke, chronic kidney disease (CKD), pulse rate,

Glasgow Coma Scale (GCS), initial mannitol dose, use of CT contrast agents within 72 hours, beta-blocker, AST, albumin, estimated glomerular filtration rate CKD Epidemiology Collaboration, serum creatinine, glucose, serum chloride, and serum sodium levels. Multivariate analysis revealed that ischemic stroke, history of CKD, GCS of 3-8, use of CT contrast agents within 72 hours, and elevated AST level were independent predictors of severe AKI. These findings offer valuable insights into pre-administration risk factors for AKI and may contribute to developing more efficient treatment strategies.

중증 신경 환자에서 만니톨 사용 후 급성콩팥손상 발생 결정요인: 만니톨 치료 전 데이터 기반 분석

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(초록)

만니톨은 외상뇌손상, 허혈뇌졸중 혹은 출혈뇌졸중 환자들에서 뇌부종 및 두개내압상승 치료로 널리 사용되지만, 고용량 및 장기간 사용 시 급성콩팥손상(Acute Kidney Injury, AKI) 등 부작용이 발생할 수 있다. 일부 연구에서 만니톨 투여 후 AKI 발생 관련 위험인자들을 조사하였으나, 대부분의 연구들은 만니톨 투여 이후 데이터를 포함하여 분석하였다. 이로 인해 만니톨 투여 전 어떠한 위험인자들이 만니톨 유발 AKI 발생에 영향을 주는 지 평가하는 데에는 한계가 있었다. 본 연구는 중증 신경 환자를 대상으로 만니톨 투여 전 어떤 요인들이 AKI 발생 위험을 증가시키는지를 조사하였다. 2018년 8월부터 2021년 6월까지 계명대학교 동산병원 신경과, 신경외과에 입원하여 뇌부종과 두개내압상승 조절을 위해 만니톨 사용한 환자들을 대상으로, 진단, 병력, 검사실 소견, 임상정보 및 치료를 후향적으로 분석하였다. 총 421명의 환자 중 367명은 비중증 AKI 그룹이었고, 54명은 중증

AKI 그룹이었다. 단일변량분석을 시행하였을 때, 비중증 AKI 그룹과 중증 AKI 그룹 사이에 유의미한 차이를 보인 변수로는 나이, 허혈뇌졸중 진단, 만성콩팥질환 과거력, 글래스고혼수척도, 첫 만니톨 투여 시 1회 투여량(g/kg), 맥박, 첫 만니톨 투여 72시간 내 CT 조영제 사용 여부, 아스파트산 아미노기전달효소, 베타차단제 사용 여부, 알부민, 혈청 크레아티닌, 추정사구체여과율, 혈당, 혈중 나트륨과 혈중 염소 수치가 통계적으로 유의한 차이가 있었다. 두 그룹 간 유의미한 차이를 보이는 변수들을 이용하여 다변량회귀분석을 시행하였을 때는 허혈뇌졸중 주진단이 있을수록, 만성콩팥질환 과거력이 있을수록, 글래스고혼수척도 점수가 3-8점일수록, 첫 만니톨 투여 72시간 내 CT 조영제를 사용했을 경우, 아스파트산아미노기전달효소 값이 높을수록 중증 AKI의 독립적인 위험인자임이 확인되었다. 이러한 결과는 만니톨 투여 전 AKI 발생 위험을 고려할 때 유용한 정보를 제공하고, 보다 효율적인 치료를 하는데 도움이 될 수 있다.