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OBSERVATIONAL STUDY

Incidence and Risk Factors for Acute Kidney Injury Following Mannitol Infusion in Patients With Acute Stroke

A Retrospective Cohort Study

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Abstract: Mannitol, an osmotic diuretic, is commonly used to treat patients with acute brain edema, but its use also increases the risk of developing acute kidney injury (AKI). In this study, we investigated the incidence and risk factors of mannitol-related AKI in acute stroke patients.

A total of 432 patients (ischemic stroke 62.3%) >20 years of age who were admitted to the neurocritical care center in a tertiary hospital and received mannitol treatment were enrolled in this study. Clinical parameters including the scores of National Institutes of Health Stroke Scale (NIHSS) at admission, vascular risk factors, laboratory data, and concurrent nephrotoxic medications were registered. Acute kidney injury was defined as an absolute elevation in the serum creatinine (Scr) level of ≥ 0.3 mg/dL from the baseline or a $\geq 50\%$ increase in Scr.

The incidence of mannitol-related AKI was 6.5% (95% confidence interval, 4.5%–9.3%) in acute stroke patients, 6.3% in patients with ischemic stroke, and 6.7% in patients with intracerebral hemorrhage. Multivariate analysis revealed that diabetes, lower estimated glomerular filtration rate at baseline, higher initial NIHSS score, and concurrent use of diuretics increased the risk of mannitol-related AKI. When present, the combination of these elements displayed an area under the receiver operating characteristic curve of 0.839 (95% confidence interval, 0.770–0.909). In conclusion, mannitol-related AKI is not uncommon in the treatment of acute stroke patients, especially in those with vulnerable risk factors.

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INTRODUCTION

Brain edema leading to increased intracranial pressure is one of the most devastating complications in patients with acute brain injury or stroke. It can lead to further neurological deterioration, a poor functional outcome, and death. Mannitol, an osmotic diuretic, has been used for decades to reduce intracranial pressure by increasing the osmotic gradient between blood and brain parenchyma, thereby promoting the transfer of water from brain tissue to the circulatory system.[1] The efficacy of mannitol in reducing intracranial pressure is dose-dependent, with higher doses delivered by rapid bolus infusion producing long-lasting reductions in intracranial pressure.[2,3] However, the use of mannitol also poses various risks that may preclude mannitol treatment, including acute kidney injury (AKI), electrolyte imbalance, volume overload, and rebound edema.[1] Actually, mannitol may not be a direct nephrotoxic agent as it did show some renal protective benefits in specific indications. Dehydration and preexisting renal impairment may be the risk to aggravate the toxicity of mannitol therapy.[4]

Mannitol-related AKI has been investigated in only a few studies.[5–7] Kim et al[5] reported recently that a high infusion rate, advanced age, and impaired renal function are risk factors for mannitol-related AKI in patients with intracranial hemorrhage. However, the general clinical relevance of that study is limited considering the small patient number and the heterogeneity of intracranial bleeding among patients in the study, which included subdural hemorrhage, epidural hemorrhage, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage. As the prognostic factors for patients with traumatic brain injury, subdural hemorrhage, epidural hemorrhage, subarachnoid hemorrhage, and brain tumor may be different from those with ischemic stroke (IS) or ICH. In the present study, we aimed to focus specifically on the incidence and risk factors for mannitol-related AKI in acute stroke patients.

METHODS

Patients

This study was performed in the neurocritical care unit of a university hospital in Taiwan. The criteria for admission to the neurocritical care unit include patients with severe neurological deficit (eg, National Institute Health Stroke Scale [NIHSS]

score higher than 8), stroke in evolution, IS patients receiving thrombolytic therapy or endovascular treatment, ICH patients receiving intensive blood pressure control, or medical conditions requiring intensive care.[8]

We conducted a retrospective review of consecutive patients >20 years of age who received mannitol therapy during January 1, 2010, to December 31, 2014, after admission to the neurocritical care unit due to IS, and nontraumatic ICH. Patients undergoing hemodialysis or peritoneal dialysis for end-stage renal disease, and those suffering from AKI before the initiation of mannitol therapy were excluded from analysis, for example, patients with a rapid change in the serum creatinine (Scr) level, which meets the Acute Kidney Injury Network diagnostic criteria before the initiation of mannitol therapy. Patients admitted for traumatic brain injury, subdural hemorrhage, epidural hemorrhage, subarachnoid hemorrhage, and brain tumor were also excluded. Mannitol (20% w/v solution; 100 mL/bottle; Taiwan) was administered via bolus intravenous infusion several times per day, the specific dosage and frequency determined by the healthcare practitioners according to the patient's clinical condition. The study protocol was approved by the National Taiwan University Hospital Research Ethics Committee (No. 201410029RINA). Inform consent for study participants was not obtained as this was a retrospective cohort study and we did no interventions except for standard poststroke treatment. Consent for publication was not obtained because our data could not be traced back to any identifiable individual.

Data Collection

We collected the following laboratory data and patient history for each individual enrolled in the study: age, gender, body height and weight, diagnosis, NIHSS score upon arrival, history of vascular risk factors (atrial fibrillation, coronary artery disease, congestive heart failure, chronic kidney disease, diabetes, hypertension, IS, transient ischemic attack, ICH, and myocardial infarction), Scr level within 3 days of admission and at the initiation and the end of mannitol treatment. Any major operation at the time of mannitol treatment was also recorded. We also collected information on the concurrent use of nephrotoxic medications during mannitol therapy, including aspirin, angiotensin-converting enzyme inhibitors, angiotensin receptor blocking agents, diuretics, nephrotoxic antimicrobial agents (ie, aminoglycosides, vancomycin, amphotericin B, acyclovir), nonsteroidal anti-inflammatory drugs, and nephrotoxic immunosuppressant agents (ie, cyclosporine, tacrolimus, sirolimus, and everolimus). Finally, we collected data on mannitol treatment: dosage, frequency, cumulative dose, and duration of therapy. To allow for interindividual comparisons, we divided the cumulative mannitol dose by body weight and duration of treatment (g/kg/day).

Study Outcomes

There were 2 study outcomes: (a) the incidence of mannitol-related AKI, and (b) the risk factors for mannitol-related AKI. Acute Kidney Injury Network diagnostic criteria were applied for AKI classification, which was defined as an absolute elevation in the Scr level of ≥ 0.3 mg/dL from baseline or an $\geq 50\%$ increase in Scr.[9] We calculated the estimated glomerular filtration rate (eGFR) by using the 4-variable Modification of Diet in Renal Disease equation: eGFR (mL/min/1.73 m^2) = $175 \times \text{Scr}^{-1.154} \times \text{age}^{-0.203} \times 1.212$ (if the patient is black) $\times 0.742$ (if female).[10]

Statistical Analysis

Descriptive statistics were used to obtain mean, median, standard deviation, and range. In univariate analysis, the baseline characteristics among patients with and without AKI were compared using Student's *t* test or the chi square test, as appropriate. Multivariate logistic regression was then used to identify the risk factors for mannitol-related AKI. Factors with *P* values < 0.05 in the univariate analysis were evaluated using multivariate regression. A receiver operating characteristic (ROC) curve was used to illustrate a predictive model of mannitol-related AKI in multivariate logistic regression. SPSS (version 12.0; SPSS Inc) was used for analysis, and values of *P* < 0.05 were considered statistically significant.

RESULTS

Incidence and Manifestations of Mannitol-Related AKI

During the study period, a total of 2518 patients were admitted to the neurocritical care unit, among whom 1748 (69.4%) were diagnosed with acute stroke and 1296 with IS (51.5%). Among the stroke patients, 542 (31.0%) received mannitol therapy. After excluding 110 patients with incomplete laboratory data, a total of 432 patients (IS: 269, 62.3%) were included for this analysis. Twenty-eight patients (13 males) developed AKI. The incidence of mannitol-related AKI was 6.5% (95% confidence interval [CI], 4.5–9.3%) among all stroke patients, 6.3% (95% CI, 4.0–10.0%) among IS patients, and 6.7% (95% CI, 3.8–11.9%) among ICH patients. There was no difference in the incidence of mannitol-related AKI between the IS and ICH groups (*P* = 0.84).

The onset, clinical manifestations, and outcomes of patients who developed mannitol-related AKI are summarized in Table 1. Seventy-eight percent of patients developed AKI within 1 week. Complete recovery with a return of eGFR to the baseline value was observed in 60.7% of patients. None of these patients required renal replacement therapy for AKI, and none of the mortality was related to AKI.

Risk Factors for Mannitol-Related AKI

Table 2 lists the baseline characteristics for patient receiving mannitol therapy. Age, gender, and stroke type were generally comparable between patients with and without AKI. Univariate analysis showed that patients with AKI had a significantly greater prevalence of diabetes and chronic kidney disease and fewer previous IS or transient ischemic attacks than those without AKI (Table 2). Acute kidney injury patients had significantly higher initial NIHSS, and analysis of laboratory data revealed that AKI patients had significantly lower hemoglobin at admission, and lower eGFR values upon arrival and at the initiation and completion of mannitol therapy compared to non-AKI patients (Table 3). Patients with AKI received significantly higher mannitol doses (g/kg/day) and a lower cumulative mannitol dose (g) and were more often prescribed concomitant diuretics (Table 4).

The results of multivariate logistic regression analysis are summarized in Table 5. Higher initial NIHSS score, lower eGFR on arrival, diabetes, and the concomitant use of diuretics significantly increased the risk of mannitol-related AKI. Higher mannitol doses (g/kg/day) showed a trend for increasing the risk, but the effect was not significant (*P* = 0.053). Figure 1 shows the ROC curve for a predictive model of mannitol-related AKI based on the parameters of initial NIHSS score, eGFR on

TABLE 1. Outcome of Patients With Mannitol-Related Acute Kidney Injury[*]

Outcome[†]		Onset of Acute Kidney Injury		Mannitol Dose, g/day	
Recovery	17 (60.7)	≤ 3 days	14 (50.0)	< 200	26 (92.9)
Do not recover	4 (14.3)	4–7 days	8 (28.6)	≥ 200	2 (7.1)
Death[‡]	7 (25.0)	≥ 7days	6 (21.4)	−	−

[*] Data are expressed as number (percentage) unless specified.
[†] None of these patients required renal replacement therapy during acute kidney injury.
[‡] Two patients discharged against the physician's advice. None of these patients died because of mannitol-related acute kidney injury.

TABLE 2. Characteristics of Patients Who Was Prescribed Mannitol[*]

	No AKI (n = 404)	AKI (n = 28)	P Value
Male	226 (55.9)	13 (46.4)	0.334
Age, y	66.1 ± 15.9	70.4 ± 15.0	0.165
Weight, kg	63.0 ± 13.2	64.9 ± 14.6	0.461
Ischemic stroke	269 (62.3)	17 (60.7)	0.843
Medical history			
Atrial fibrillation	82 (20.3)	5 (17.9)	1.0
Congestive heart failure	19 (4.7)	4 (14.3)	0.053
Chronic kidney disease	9 (2.2)	7 (25.0)	<0.001
Diabetes mellitus	90 (22.3)	15 (53.6)	0.001
Hypertension	267 (66.1)	20 (71.4)	0.681
Myocardial infarction or coronary artery disease	47 (11.6)	5 (17.9)	0.362
Old intracerebral hemorrhage	28 (6.9)	0 (0)	0.241
Old stroke or transient ischemic attack	72 (17.8)	1 (3.6)	0.033
Recent surgery	54 (13.4)	1 (3.6)	0.234

AKI = acute kidney injury.
[*] Data are expressed as number (percentage) or mean ± standard deviation unless specified.

TABLE 3. Associated Data of Patients Who Was Prescribed Mannitol[*]

	No AKI (n = 404)	AKI (n = 28)	P Value
At admission			
Systolic blood pressure, mm Hg	165.1 ± 36.9	174.3 ± 44.4	0.210
Diastolic blood pressure, mm Hg	95.6 ± 21.7	97.1 ± 26.3	0.733
Hemoglobin, g/dL	14.0 ± 2.2	12.9 ± 2.1	0.006
NIHSS score	17 [0,38]	21 [9,38]	0.034
Proteinuria (positive)	225 (55.7)	21 (75.0)	0.160
eGFR, mL/min/1.73 m^2			
On arrival	81.7 ± 28.6	61.9 ± 36.6	0.001
At the starting of mannitol	84.8 ± 30.6	63.5 ± 38.0	<0.001
At the end of mannitol	98.1 ± 35.5	37.0 ± 22.7	<0.001

AKI = acute kidney injury, eGFR = estimated glomerular filtration rate, NIHSS = National Institute of Health stroke scale.
[*] Data are expressed as number (percentage), mean ± standard deviation, or median [range] unless specified.

arrival, diabetes, and concomitant use of diuretics. The area under the ROC curve was 0.839 (95% CI, 0.770–0.909). Furthermore, subgroup analysis on different types of stroke showed that concomitant use of diuretics in both IS and in ICH patients were independently associated with mannitol-related AKI: IS, relative risk = 4.38, $P = 0.008$; ICH, relative risk = 50.4, $P < 0.001$; and diabetes mellitus in ICH patients, relative risk = 14.04, $P = 0.019$.

In subgroup analysis, diabetes remained a significant risk factor for mannitol-related AKI in both IS and ICH patients. Concomitant use of diuretics significantly increased the risk for mannitol-related AKI in ICH patients (Table 6).

TABLE 4. Information About Mannitol and Concurrent Medications[*]

	No AKI (n = 404)	AKI (n = 28)	P Value
Mannitol			
Dosage, g/kg/day	0.9 ± 0.5	1.3 ± 1.7	0.002
Accumulative dosage, g	361.7 ± 281.5	236.8 ± 174.6	0.021
Concurrent medications			
Aspirin	24 (5.9)	0 (0)	0.389
ACEi	16 (4.0)	0 (0)	0.614
ARB	119 (29.5)	6 (21.4)	0.518
Diuretics	71 (17.6)	17 (60.4)	<0.001
Antibiotics[†]	25 (6.2)	0 (0)	0.393
NSAID	38 (9.4)	2 (7.1)	1.000
Immunosuppresant drugs[‡]	0 (0)	0 (0)	–
Inotropic agents	28 (6.9)	2 (7.1)	1.000

ACEi = angiotensin-converting enzyme inhibitors, AKI = acute kidney injury, ARB = angiotensin receptor blocking agents, NSAID = nonsteroidal antiinflammatory drugs.
[*] Data are expressed as number (percentage) or mean ± standard deviation unless specified.
[†] Nephrotoxic antibiotics: aminoglycosides, vancomycin, colistin, amphotericin B, and acyclovir.
[‡] Nephrotoxic immunosuppresants: cyclosporine, tacrolimus, sirolimus, and everolimus.

DISCUSSION

This study was the first of its kind to investigate the incidence and risk factors for mannitol-related AKI exclusively in acute stroke patients. The results revealed 2 important findings. First, the incidence of mannitol-related AKI was 6.5% and did not differ significantly between patients with IS and ICH. Second, we identified diabetes, reduced baseline eGFR, higher initial NIHSS score, and concurrent use of diuretics as independent risk factors for mannitol-related AKI.

Previous studies have reported the incidence of mannitol-related AKI ranges from 10.5% to 20.3% among different patient cohorts.[5,7,11] However, our analysis revealed a lower occurrence (6.5%), despite the high proportion of elderly individuals in our patient cohort (age ≥70 years, 46.8%). There may be several factors contributing to the relatively low

TABLE 5. Multivariate Regression for Mannitol-Related Acute Kidney Injury

Covariate	Odds Ratio	95% CI	P Value
Age, y	0.99	(0.96, 1.02)	0.347
Male sex	0.94	(0.38, 2.34)	0.900
NIHSS score[*]	1.06	(1.00, 1.11)	0.048
eGFR, mL/min/1.73 m^2[*]	0.98	(0.96, 1.00)	0.036
Diabetes mellitus	3.62	(1.47, 8.93)	0.005
Diuretics use	8.50	(3.46, 20.86)	<0.001
Mannitol dosage, g/kg/day	1.58	(0.99, 2.53)	0.053

CI = confidence interval, eGFR = estimated glomerular filtration rate, NIHSS = National Institute of Health Stroke Scale.
[*] NIHSS score and eGFR at admission.
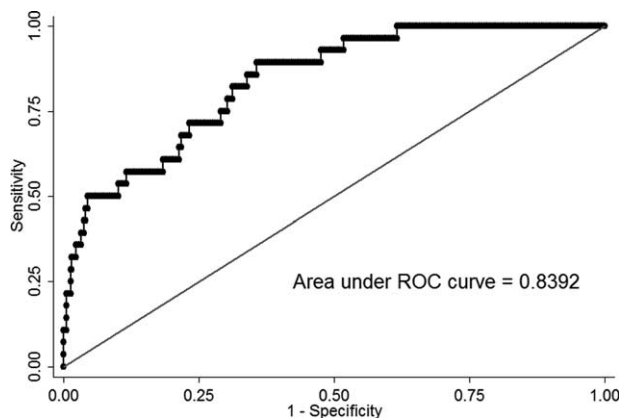
FIGURE 1. Receiver operating characteristic curve for prediction of mannitol-related acute kidney injury.

incidence of mannitol-related AKI in this study. First, as the harmful effect of mannitol is reported to be dose-related, daily doses of ≥200 g or a cumulative doses of >1100 g should be discouraged.[12] Most of our patients received mannitol treatment with doses below the aforementioned 200-g daily dose (1.3%) as well as the 1100-g cumulative dose (2.4%). Second, most mannitol-related AKI occurred in patients who received mannitol to treat brain edema or increased intraocular pressure.[13] Whether there is difference in the incidence of mannitol-related AKI between patients with various etiologies such as acute stroke, head injury, or whether it was affected by the severity of brain edema needs to be clarified.

The pathogenesis of mannitol-related AKI is not fully understood. Proposed mechanisms include (a) renal vasoconstriction produced by a high dose/concentration of mannitol; (b) profound diuresis and natriuresis; and (c) isomeric tubular

TABLE 6. Multivariate Regression for Mannitol-Related Acute Kidney Injury: Subgroup. Analysis Among Patients With Ischemic Stroke and Intracerebral Hemorrhage

Covariate	Odds Ratio	95% CI	P Value
Ischemic stroke			
Age, y	1.01	(0.96, 1.05)	0.749
Male sex	0.76	(0.22, 2.60)	0.660
NIHSS score[*]	1.05	(0.97, 1.14)	0.268
eGFR, mL/min/1.73 m^2[*]	0.98	(0.96, 1.01)	0.168
Diabetes mellitus	2.82	(0.91, 8.70)	0.071
Diuretics use	4.74	(1.57, 14.36)	0.006
Mannitol dosage, g/kg/day	1.93	(0.95, 3.94)	0.070
Intracranial hemorrhage			
Age, year	0.95	(0.89, 1.01)	0.109
Male sex	0.46	(0.07, 2.96)	0.411
NIHSS score[*]	1.06	(0.98, 1.14)	0.148
eGFR, mL/min/1.73 m^2[*]	0.99	(0.96, 1.02)	0.335
Diabetes mellitus	12.76	(1.33, 122.26)	0.027
Diuretics use	47.77	(5.65, 403.99)	<0.001
Mannitol dosage, g/kg/day	0.66	(0.08, 5.51)	0.700

CI = confidence interval, eGFR = estimated glomerular filtration rate, NIHSS = National Institute of Health stroke scale.
[*] NIHSS score and eGFR at admission.

vacuolization or tubular cell swelling, that is, so-called osmotic nephropathy.[13–15] Furthermore, patients with preexisting risk factors such as advanced age, underlying kidney disease, and concomitant use of nephrotoxic agents have been shown to be predisposed to the development of drug-related osmotic nephropathy.[12,16] Our results were similar in this regard. Reduced baseline eGFR and concurrent use of diuretics were independent risk factors for mannitol-related AKI. Mannitol is freely filtered through glomerular filtration with limited reabsorption.[13] In renal impairment, the half-life of mannitol can increase from 70 to 100 min to >36 h.[13,14] As a result, it is possible for mannitol to accumulate, leading to harmful effects. Furthermore, mannitol induces a marked reduction in water and salt reabsorption along the entire renal tubule. The increase in water and salt delivery from the proximal tubule actually leads to enhancement of sodium reabsorption at Loop of Henle, distal tubule, and collecting duct.[13] Nevertheless, concomitant use of diuretics abolishes the compensatory effect and causes profound diuresis, volume depletion, and, more devastating, AKI.[12,14] The results for subgroup analysis were similar between patients with IS and ICH, indicating the important role of diuretics in the development of mannitol-related AKI.

Acute kidney injury is not an uncommon complication after stroke. Furthermore, a high NIHSS score was previously reported to be a risk factor for AKI after stroke.[17] We excluded patients who developed AKI before mannitol treatment, and still found the association between stroke severity and development of mannitol toxicity. On the other hand, the association between diabetes and nephrotic complications has been well established. Moreover, diabetic patients have been reported to be at a higher risk of AKI.[18] Renal hemodynamics in diabetic patients appears to be different from that in nondiabetic individuals. The increase in renal blood flow after mannitol administration is accompanied by a redistribution of renal blood flow, which leads to reduced oxygen delivery to the medulla and predisposes patients to ischemic renal injury.[19,20] In support of these points, our result showed that a high NIHSS score and the presence of diabetes were 2 independent risk factors for mannitol-related AKI.

Regarding the clinical course, more than half of our patients developed AKI within 1 week of mannitol therapy,[14,21] and ∼60% of them recovered to the baseline renal function after discontinuation of mannitol. Early interruption of mannitol treatment may be the main cause of lower accumulative mannitol dose in the AKI group. Management of mannitol-related AKI includes discontinuing mannitol treatment and starting dialysis if clinically indicated. This adverse reaction usually responds to prompt removal of mannitol.[13] Although mannitol-related AKI can be transient, the association between AKI after stroke and poor clinical outcome has been mentioned in several studies.[17,22] Physicians should be aware that a patient's underlying condition and commitment medications may exacerbate the risk of mannitol therapy.

We acknowledge the following limitations of this study. First, the decision to initiate mannitol therapy and the mannitol doses varied according to the physician's expertise. As patients with worse baseline renal function tended to receive lower doses of mannitol for shorter durations, and this may lead to an underestimation of the incidence of mannitol-related AKI. Second, this is a retrospective study, and patients with missing data were excluded from analysis. Third, outcome after acute stroke was not included in the present study. Actually, it is not appropriate attribute stroke outcome to mannitol-related AKI. Cormobidities, medications, and laboratory tests all affects stroke outcome.[23,24] Fourth, the causative relationship between concurrent medications and the development of mannitol-related AKI could not be easily clarified. A further prospective study is necessary to validate the results of our findings.

CONCLUSIONS

Patient-specific factors including diabetes, underlying renal impairment, high initial NIHSS scores, and concurrent use of diuretics were associated with an increased risk of developing mannitol-related AKI. Physicians should pay close attention to these patients as the toxicity of mannitol therapy may be exaggerated.

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