Changes of Ureum-Creatinin Level in Acute Stroke Patients Treated with Mannitol in Department of Neurology, Medical Faculty University of Sumatera Utara Haji Adam Malik Hospital Medan – Indonesia

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Result: of 25 patients (16 males, 9 females); 9 patients had acute ischemic stroke and 16 had acute hemorrhage stroke. Increasing of serum ureum level 1.40 times was observed on the 2nd day (p< 0.05) and 2.01 times on the 5th day (p< 0.05) and serum creatinin level was increased 1.32 times on the 2nd day (p< 0.05) and 1.85 times on the 5th day (p < 0.05) compared with the value before administration. Conclusion: mannitol 20% administration for acute stroke patients with increased intracranial pressure showed increasing of serum ureum-creatinin level significantly (p<0.05).

Keywords: ureum-creatinin, acute stroke, mannitol


Kata kunci: ureum-kreatinin, stroke akut, manitol
INTRODUCTION

In Indonesia according to Family Health Survey on 1995, stroke was one of the main cause of mortality and disability which has to be treated, immediately and accurately.1

Many factors influence the outcome of stroke patients. One of them is complication in either acute phase or rehabilitation periods. Complication can be serious, causing death. Common cause of these in stroke patients, cerebral edema, heart disease, and pulmonary emboli dominate in the first week.2

The most lethal complication of stroke is brain edema after large ischemic and hemorrhagic stroke. In stroke units, brain edema, pulmonary embolism, and cardiac abnormalities are the major causes of early death.2,3

Intra cerebral hemorrhages, wide infarct with cerebral edema cause compression structures on brain, increase intracranial pressure and can cause herniation. For decrease this effect cerebral edema therapy should begin as soon as possible.3

Brain edema begins to develop in the brain tissues surrounding the hematoma within the first several hours after intracranial hemorrhage. A hematoma combined with brain edema causes compression of the surrounding brain structures and elevation of intracranial pressure.4

Mannitol is used worldwide to treat acute stroke patients, although its efficacy and safety have not been proven by randomized trials, thus mannitol usage in therapy still controversial. Clinical observation could not prove the beneficial effect of mannitol in ischemic or hemorrhage stroke in humans.5

Mannitol is widely used to decrease intracranial pressure and to alleviate the space occupying effect of the brain hematoma.6

Mannitol is reported to decrease cerebral edema, infarct size, and neurological deficit in several experimental models of ischemic stroke.7

Numerous studies confirm the nephrotoxic potential of mannitol especially in patients with renal insufficiency, and also in patients with cranio cerebrospinal trauma without previous kidney failure. Pathogenesis of mannitol induced renal failure is not established but may be associated with renal vasoconstriction produced by high concentration of mannitol.8

The most common complications of mannitol therapy are fluid and electrolyte imbalances, cardiopulmonary edema, rebound cerebral edema, and seldom hypersensitivity reaction.

Mannitol can also cause renal failure even in therapeutic doses.3,6,7,8

How ever the influence of osmotherapy on renal function in patients treated with mannitol due to increased intracranial pressure was not so far well described.9

T. Dziedzic et al in 2000, performed studied on 51 patients with intra cerebral hemorrhage primer, all of the patients was treated with mannitol 20% (0.25-0.5) mg/kg/every 4 hours and furosemide 10mg every 8 hours, mannitol was given for no longer than 5 days and analysis the influences ureum-creatinin serum concentration before mannitol administration compared with 2nd days, 5th days, and 14th days.

The conclusion from that study was increased ureum – creatinin serum concentration after mannitol therapy on 2nd days and 5th days.9

The aim of this study was to determine the influence of mannitol therapy on renal function with evaluate changes of ureum-creatinine serum level after mannitol therapy in acute stroke patients.

METHODS AND MATERIALS

This study was performed in neurology ward of RSUP H. Adam Malik Medan since January 2nd 2005 to April 30th 2005, on all acute stroke patients with raised intracranial pressure who fulfilled the inclusion and exclusion criteria. The inclusion criteria is all the acute stroke patients who have been treated with mannitol and exclusion criteria is stroke patients who are contraindicated for mannitol such as renal failure, cardiac failure, dehydrated, diabetes mellitus, and acute stroke patients who administrated nefrotoxic drugs (include antibiotic)

The research was an intervention of data collecting through prospective study.

All the patients were checked up according to standarized protocol in Department of Neurology, Medical Faculty University of Sumatera Utara Haji Adam Malik Hospital, Medan Indonesia.

These check-ups consisted of complete urine-blood-feces test, glucose nuchter and 2 hours post prandial, lipid profile, ureum-
creatinin. Uric acid, electrolyte, and liver function test, CT scan within 24 hours, thorax photo, electrocardiography, and fluid balance.

If Glomerular Filtration Rate (GFR) is less than 15 during a mannitol administration, the patients is disqualified from research.

GFR is gotten from \((140\text{-age})\times 72\div \text{Serum creatinin}\). For Women creatinin clearance \(X 0.85\).\(^{10, 11}\)

Patients fulfilled inclusion criteria were given mannitol according to protocol in Department of Neurology, Medical Faculty University of Sumatera Utara Haji Adam Malik Hospital Medan Indonesia in doses 125 cc/6 hours/IV in 30 minutes. Serum ureum-creatinin is known before the administration, second and fifth day after administration of mannitol.

All hypertension patients were given ACE inhibitor Captopril.

Serum ureum-creatinin was measured using Automatic analysis Hitachi 902 machine.

Mannitol was mannitol 20% Otsuka's production.

To assess the outcome, Barthel index and Glasgow Outcome Scale were used.

Statistical for Windows version 10.5 use to analyze the difference of mean of ureum-creatinin level between before administration and second and fifth day, we used Anova test since the variance were that same and Multiple Comparisons Post Hoc Tests. To analyze the influence of age toward changes of serum ureum-creatinin level Pearson Correlation test were used. To analyze the influence of sex toward changes of serum ureum-creatinin level T-test were used.

To analyze the outcome after mannitol administration with Barthel index and Glasgow Outcome Scale Wilcoxon Signed Ranks Test were used. The level of significance was set at \(p<0.05\).

Normal adult ureum level: 10-20 mg/dl or 3.6-7.1 mmol/L (SI units). Normal adult creatinin for woman: 0.5-11mg/dL or 44-94 (micro mol/L SI units), men 0.6-1.1 mg/dL.\(^{11}\)

### RESULTS

From 82 acute stroke patients (47 ischemic stroke, 35 hemorrhagic), we found that 25 patients were administered mannitol (9 ischemic stroke, 16 hemorrhagic stroke).

### Table 1.

<table>
<thead>
<tr>
<th>Demographic and characteristics in 25 acute stroke patients after mannitol administration</th>
<th>Ischemic stroke(n=9) (36%)</th>
<th>Hemorrhage stroke(n=16) (44%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- male</td>
<td>5 (20%)</td>
<td>11 (44%)</td>
</tr>
<tr>
<td>- female</td>
<td>4 (16%)</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- &lt; 45 year</td>
<td>3 (12%)</td>
<td></td>
</tr>
<tr>
<td>- 45-55 year</td>
<td>9 (36%)</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>- &gt; 55 year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP* on admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Normal</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>- H.* mild</td>
<td>1 (4%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>- H. moderate</td>
<td>4 (16%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>- H. severe</td>
<td>1 (4%)</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>- H. very severe</td>
<td>2 (8%)</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>- Yes</td>
<td>8 (32%)</td>
<td>15 (60%)</td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 13-15</td>
<td>8 (32%)</td>
<td>14 (56%)</td>
</tr>
<tr>
<td>- ≤ 8</td>
<td>1 (4%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- yes</td>
<td>1 (4%)</td>
<td>8 (32%)</td>
</tr>
<tr>
<td>- no</td>
<td>7 (28%)</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- cerebral herniation</td>
<td></td>
<td>8 (32%)</td>
</tr>
<tr>
<td>- respiratory failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (4%)</td>
<td></td>
</tr>
</tbody>
</table>

* BP=Blood pressure  
* H=Hypertension
Most of the patients were male 16 (64%). Mean age of patients was 57.84 year (38–76), with the most age group 45-55 years 16 (64%). Patients with hypertension at admission were found 23 (92%) and most of them had hemorrhagic stroke 15 (60%). All patients who were admitted had loss of consciousness, 22 (88%) patients had Glasgow Coma Scale (GCS) score 9-11. Of 25 patients, 9 (36%) patients died and most of them, 8 (88%) had hemorrhagic stroke. Mostly, the cause of death were cerebral herniation 8 (88%) and respiratory failure was 1 (12%) patients.

Mean serum ureum concentration was 33.5 ± 11.3 mg % before mannitol administration and increased to 46.8 ± 13.4 mg% on the second day and 67.6 ± 18.0 mg % on the fifth day after mannitol administration.

Mean score of serum creatin in was 0.90 ± 0.23 mg % before mannitol administration and increased to 1.19 ± 0.36 in second day and 1.67 ± 0.48 mg% in the fifth day after mannitol administration.
After statistical analysis was done there was a significant elevation in serum ureum concentration before mannitol administration than on the second day (p < 0.05) and on the fifth day (p < 0.05) after mannitol administration. Serum ureum level elevated for 1.4 times on the second day (p < 0.05) and 2.01 times on the fifth day (p < 0.05) (Figure 1).

Statistical analysis showed a significant increased between creatinin concentration before and after administration mannitol in the second and in the fifth day (p < 0.05).

Serum creatinin level increased in to 1.32 times on the second day and 1.85 times on the fifth day (p < 0.05) compare with before mannitol administration (Figure 2).

There was any correlation between age and changes serum ureum-creatinin level on second day and fifth day after mannitol administration (p > 0.05).

There was no correlation between sex and changes of serum ureum-creatinin level on the second and fifth day after mannitol administration (p > 0.05).

Barthel index assessed on day-0 overall is 25 (100%) on 7th day, 22 (88%) bad and 3 died (12%). Where as on 14th day Barthel Index bad 13 (59%), moderate 3 (13%) and died was 6 (28%).

Glasgow Outcome Scale assessed on 14th day was death 9 (36%), severe disability 13 (52%) and moderate disability 3 (12%).

There were no significant change in Barthel index Score and Glasgow Outcome Scale (p > 0.05).

Table 2.
Barthel Index value and glasgow outcome scale in 25 acute stroke patients

<table>
<thead>
<tr>
<th></th>
<th>day-0 n( %)</th>
<th>day-7 n(%)</th>
<th>day-14 n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barthel index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- bad</td>
<td>25(100)</td>
<td>22(88)</td>
<td>13(52)</td>
</tr>
<tr>
<td>- moderate</td>
<td></td>
<td></td>
<td>3(12)</td>
</tr>
<tr>
<td>- excellent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow Outcome scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- death</td>
<td></td>
<td></td>
<td>9(36)</td>
</tr>
<tr>
<td>- severe disability</td>
<td></td>
<td></td>
<td>13(52)</td>
</tr>
<tr>
<td>- moderate disability</td>
<td></td>
<td></td>
<td>3(12)</td>
</tr>
</tbody>
</table>

Table 3.
Renal disease stadium according to GFR in 25 acute stroke patients

<table>
<thead>
<tr>
<th></th>
<th>Stadium 1* n (%)</th>
<th>Stadium 2 n (%)</th>
<th>Stadium 3 n (%)</th>
<th>Stadium 4 n (%)</th>
<th>Stadium 5 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment mannitol</td>
<td>5 (20)</td>
<td>12 (48)</td>
<td>8 (32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd day</td>
<td>4 (16)</td>
<td>3 (12)</td>
<td>18 (72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5th day</td>
<td>2 (8)</td>
<td>1 (4)</td>
<td>19 (76)</td>
<td>3 (12)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation GFR= Glomelural filtration Rate
Stadium 1= Renal impairment with normal GFR ≤ 90
Stadium 2 = mild impairment with GFR 60-90
Stadium 3 = moderate impairment GFR 30-59
Stadium 4 = severe impairment GFR 15-29
Stadium 5 = Renal failure GFR < 15
Abbrevation GFR = Glomelural filtration rate
DISCUSSION

There are two main categories in which predisposition to renal damage is increased, firstly, patients with impaired renal perfusion pressure due to sodium depletion, diuretic therapy, low cardiac output or any other condition that tends to promote increased sodium reabsorption and secondly, patients with already impaired renal function, vascular disease, severe infection, diabetes mellitus, or liver disease.

From this study, 25 patients (man 16, woman 9) aged 38-76 years (mean 57.4 ± 10.0 years) with acute stroke (9 ischemic stroke, 16 hemorrhagic stroke), this number differ from previous study by T. Dziedzic on 2000, where they found 51 patients (29 man, 22 woman) aged 28-86 years (mean 64.6 ± 12.7 years) with supratentorial intra cerebral hemorrhagic.

The small sample in this study compared to other previous studies is one of the limitation of this study. In this study, samples were acute ischemic and hemorrhage patients, while in previous studies were only toward hemorrhage stroke. Overall will shows different response on mannitol administration as anti edema.

In this study there were 23 (92%) hypertension patients and the most were hemorrhage stroke patients 15 (60%). This is probably due to hidden changes in kidney, in this case patients have a tendency on having renal failure during therapy. J.A Withworth reported analysis toward 83 patients with accelerated hypertension, found underlying cause (usually renal) for hypertension.

If operational definition of acute renal failure is Glomerular Filtration Rate (GFR) is < 15, no patient suffered from renal failure after mannitol administration on the fifth day. But tendency toward that was present, where 3 (12%) patients with severe GFR reduction (stadium 4) and 19 (76%) with moderate GFR reduction (stadium 3) see Table 4.

Although serum ureum-creatining concentration increased during mannitol administration, during therapy no patients with oliguria or anuria was present.

T. Dziedzic et al found 76% of 51 hemorrhage stroke patients suffered from renal failure after mannitol 20% administration on the fifth day. Meanwhile, Dorman HR found 8 cases of acute renal failure induced by mannitol administration for more than 3.5 ± 1.5 days.

During mannitol administration, serum ureum level increased 1.4 times on the second day (p < 0.05) and 2.01 times on the fifth day (p < 0.05). Serum creatinin level increased 1.32 times on the second day (p < 0.05) and 1.85 times on the fifth day (p < 0.05). These finding were similar to the finding by T. Dziedzic on 2000, where they found serum ureum level increase 1.5 times on the second day (p = 0.0001) and 2.3 times on the fifth day (p = 0.00001) while serum creatinin level 1.2 times on the second day (p = 10^-5) and 1.3 times on the fifth day (p = 10^-5). It shows that mannitol administration during therapy caused increasing of serum ureum-creatinin level.

All patients were admitted with unconsciously. Twenty two (88%) had Glasgow Coma Scale of 9-12 and 2 (12%) had Glasgow Coma Scale <8. During mannitol therapy, 9 (36%) patients died. This is similar to previous study by T. Dziedzic that found 20 (39%) patients died from 51 patients who were given mannitol. Considering the high mortality with the most caused by cerebral herniation 8 (88%). We questioned whether mannitol was useful in decreasing intracranial pressure by reducing mid line shift.

A Glasgow Coma Scale score of less than 8, a wide pulse pressure, a large hemorrhage, and intra ventricular extension indicate poor prognosis.

E.M. Manno et al did a study to investigated the effect of mannitol administration on cerebral edema after large infarct on cerebral hemisphere, from 7 patients it,s concluded that mannitol administration didn't change midline tissue shift or neurological deficit worsening (effect of mannitol).

We assessed the out come using Barthel index on the admission day, the seventh day and fourteenth day and Glasgow Outcome Scale on the seventh day and fourteenth day.

Barthel index score on the fourteenth days was still bad (0-65) on 13 (59%) patients and moderate (60-90) on 3 (13%). While Glasgow Outcome Scale on the fourteenth day was death 9 (36%), severe disability 13 (52%) and moderate disability 3 (13%).

This score is probably due to the early scoring of outcome for 2 weeks after onset. This score could be change if the scoring was done 3 months later.
CONCLUSION
1. There is a significant change in serum ureum-creatinin level after mannitol 20% administration.
2. There are no correlation between age, sex and serum ureum-creatinin level after mannitol administration.
3. There are no significant change in Barthel index Score and Glasgow Outcome Scale.

COMMENT
1. Mannitol administration to the acute stroke patients should be carefully especially to the hypertension and diabetes mellitus patients
2. During mannitol administration we should check renal function as control.
3. We need further studies with a larger sample.

REFERENCES