The Early Response of Mannitol Infusion in Traumatic Brain Injury

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Abstract-

Introduction: Mannitol was used in traumatic brain injury but controversy about the onset and duration.

Setting: Clinical observational study.

Methods: Fourteen traumatic brain injured patients with a Glasgow Coma Scale (GCS) score ≤ 8 were enrolled. Group I patients (n=8) with intracranial pressure (ICP) < 20 mmHg, and group II patients (n=6) with ICP ≥ 20 mmHg underwent transcranial Doppler (TCD) monitoring and blood samples were drawn every 5 minutes during the post-operation period. Several parameters were compared with statistical analysis between both groups.

Results: The ICP declined during a 30-minute recording in both groups and the decline of ICP was significant ($p < 0.05$) at the 10-minute interval in group II. The decline of hemoglobin (Hb) and oxygen content (CaO_2), increase of venous pressure (CVP) and O_2-transport ability ($CeDO_2$) at 10-minute were also statistically significant ($p < 0.05$) in group II as compared to the group I. Using a regression model between both comparisons, several parameters were statistically different at the 10-minute interval after mannitol infusion.

Conclusions: The dynamic responses can happen as early as 5-10 minutes after mannitol infusion, and had a greater effect on traumatic brain injury patients with ICP ≥ 20 mmHg. It demonstrated a significant dynamic difference between both groups. All these changes can be monitored by TCD and peripheral blood tests.

Key Words: Mannitol infusion, Early response, Trascranial Doppler

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INTRODUCTION

Infusion of hypertonic mannitol solution has been used for reducing high intracranial pressure (ICP) in patients with traumatic brain injuries (TBI)[1-4] or large-scale cerebral occlusive diseases[5-7]. The presumed mechanisms of action reported include osmotic dehydration, shrinkage of brain parenchyma[8], and co-existence of the rheological effects to improve cerebral blood flow[9-12]. The mannitol effect estimated from 30

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minutes to 2-4 hours has been mentioned in the literature [7-9]. However, the response in the early period of mannitol infusion is not well studied.

The cerebral blood flow velocities of the main vessels in the Willis circle can be monitored by low-frequency 2MHz pulse-wave transcranial Doppler (TCD) [13]. At present, TCD is commonly accepted as a simple and noninvasive method to evaluate the serial hemodynamic changes in TBI patients in intensive care unit[14-16]. TCD is a non-invasive ultrasonic technique that measures local blood velocity and direction in the proximal portions of large intra-cranial arteries. It is convenient and inexpensive, and can be used in the detection of cerebral flow velocity. The aim of our study is to evaluate the early effect of mannitol infusion using TCD for continuous measurement, and evaluate the systemic changes by drawing peripheral venous and arterial blood. We speculate the onset of mannitol effects can occur within 30 minutes in reducing ICP, and we also try to explain the mechanisms of reducing ICP by improving the cerebral flow dynamics.

MATERIAL AND METHODS

During the period from January 1, 2005 to July 30, 2005, fourteen patients with TBI of subdural hemorrhage (GCS scores < 8) underwent emergent craniotomy were enrolled for this study. This study was approved by the Ethics Committee of Chi-Mei hospital. All subjects received standard management to keep adequate cerebral perfusion pressure (CPP) of > 60 mmHg. All patients were sedated using propofol (0.5-6 mg/kg/hr) with or without atracurium (0.3-1.2 mg/kg/hr) during the postoperative period and during TCD monitoring for 30 minutes. An ICP microsensor (Codman and Shurtlef, Inc., Rayman, MA) was placed into the ipsilateral frontal parenchyma during surgery to monitor ICP. The mean arterial blood pressure (MAP) and central venous pressure (CVP) were monitored and recorded by standard pressure transducers. The cerebral perfusion pressure (CPP) was calculated by mathematic transformation of MAP minus ICP. All pressures and dynamic changes were displayed on computerized oscilloscopes.

Continuous TCD monitoring

TCD (Multi-Dop X_2, DWL, Elektronische Systeme Gmbh, Germany) was used for monitoring, and measuring the cerebral blood flow velocity of the middle cerebral artery on the lesion side. A 2-MHz probe was placed over the operation side using a fixed elasticized band with a good insonated angle to detect cerebral blood flow. Signals were obtained through temporal window for the MCA at a depth between 50 and 60 mm for 30 minutes by an experienced technician[13]. The recording was terminated if any disturbance occurred to avoid outlier or artificial bias. All selected subjects were recorded well without difficulty. The cerebral vascular resistance (CVR) was estimated as CPP divided by mean velocity of MCA (CPP/VmMCA)[11,17]. The higher CVR meant the lower VmMCA, which indicating that cerebral perfusion was insufficient due to inadequate MCA flow volume.

Mannitol infusion study

A standard dosing of single bolus of 0.5 g of mannitol per kg[1,9] was administered over 5 minutes via a peripheral venous line in all patients. The baseline values of ICP, MAP, CPP and CVP were obtained before mannitol infusion. Recording maintained for 30 minutes after mannitol infusion. Venous blood was sampled for measurement of hemoglobin (Hb), and arterial blood was sampled for partial pressure of O_2 (PaO_2), and O_2 saturation. The oxygen content was calculated as CaO_2 = (Hb$\times O_2$ saturation$\times$1.36) + $PaO_2\times$0.003, and equivalent of cerebral O_2-transport ($CeDO_2$) was calculated as $CaO_2\times$VmMCA by mathematic transformation according to previous report in the literature[18]. The need of O_2 transport depended on flow velocity of the MCA and the red blood cells concentration. The lower Hb carrying less O_2 reflected the needs of higher VmMCA and higher O_2 transport ($CeDO_2$) to the brain[18,19]. Measurements of these variables were obtained every 5 minutes for 30 minutes. The monitoring was recorded carefully to avoid interference and keep the curving line stable.

Subjects were divided into group I with ICP < 20 mmHg and group II with ICP ≥ 20 mmHg. The means with standard errors for individual data before and after

mannitol infusion were plotted. The extreme data or outlier was evaluated by a neurologist who was skillful in TCD to exclude artificial values. One-way analysis of variance (ANOVA) and linear regression modeling were used for statistical analyses. All data were input into a computer for analysis with SPSS version 10 (SPSS Inc, Chicago, Illinois, USA). Probability values of $p < 0.05$ were considered statistically significant.

RESULTS

Totally 14 patients of TBI with GCS scores ≤ 8 were studied. Eligibilities were divided into group I with ICP < 20mmHg (n=8, 4 women and 4 men, mean age 37.5±14.6 years) and group II with ICP ≥ 20 mmHg (n=6, 2 women and 4 men, mean age 40.1±14.3 years). Since time difference would affect ICP slope and the stability of MCA velocity. The time elapsed from head injury to the time of TCD performance was 54.4±3.2 hours in group I compared to 56.6±2.5 hours in group II. There was no statistical difference in this time difference.

The time course for MAP, CPP, ICP and CVP changes after mannitol infusion in group I is shown in Fig. 1. There was a tendency for MAP, CPP and CVP to

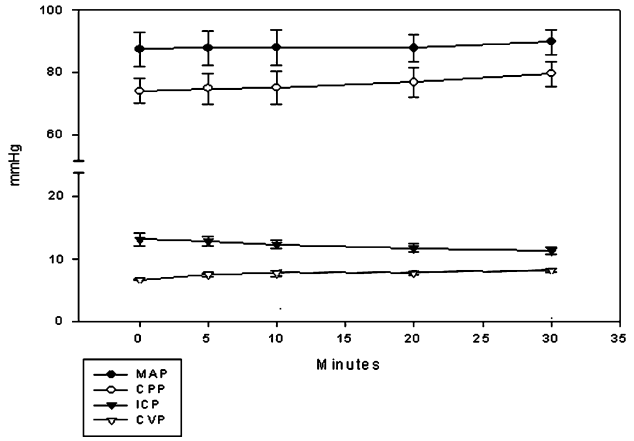

Figure 1. MAP, CPP, ICP, and CVP for ICP < 20 mmHg within 30 minutes' post-mannitol infusion.
MAP: mean artery pressure; CPP: cerebral perfusion pressure; ICP: intracranial pressure; CVP: central venous pressure. No significant differences by time lapsed.

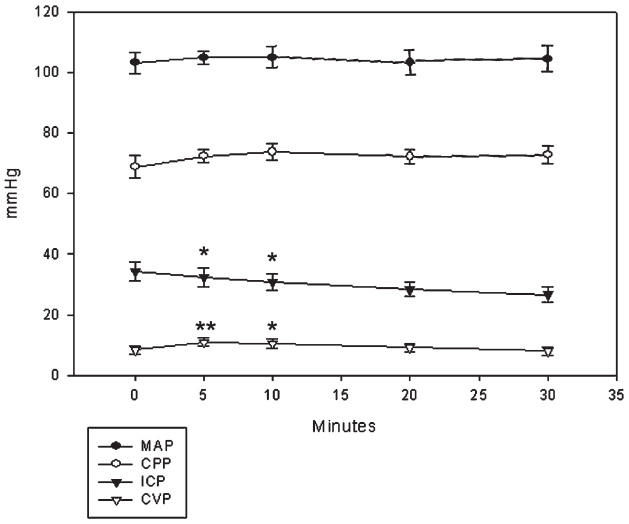

Figure 2. MAP, CPP, ICP, and CVP for ICP ≥ 20 mmHg within 30 minutes' post-mannitol infusion.
MAP: mean artery pressure; CPP: cerebral perfusion pressure; ICP: intracranial pressure; CVP: central venous pressure.
*p < 0.05; **p < 0.01; within-subject effect compared to time zero, repeated ANOVA.

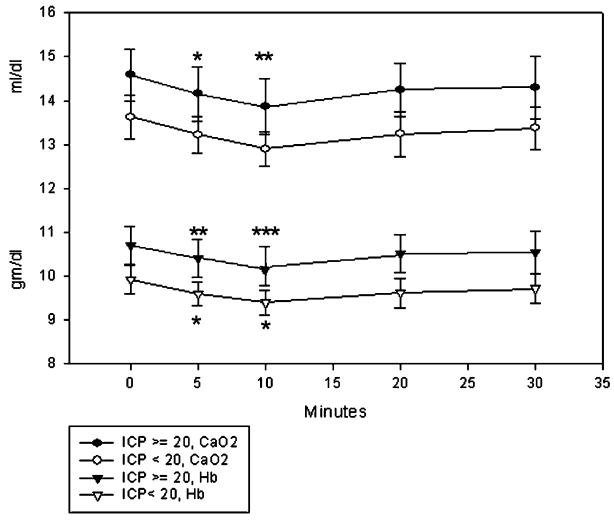

Figure 3. Hemoglobin (Hb) and arterial O_2 content (CaO_2) changes of post-mannitol infusion on TBI patients with ICP < 20 or ≥ 20 mmHg.
*p < 0.05; **p < 0.01; ***p < 0.001, within-subject effect compared to time zero, repeated ANOVA.

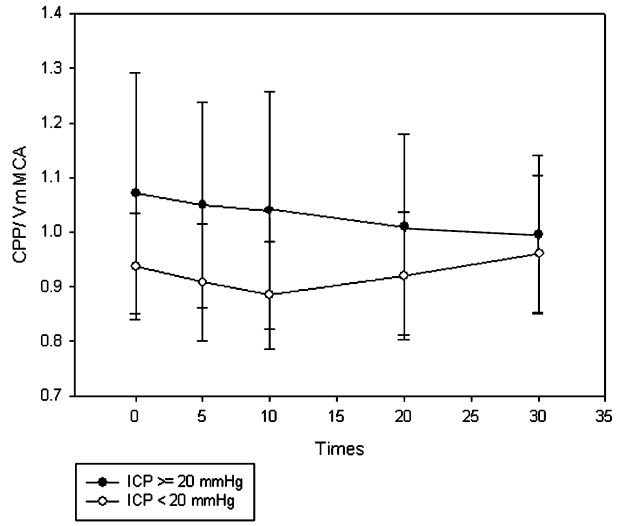

Figure 4. Change in cerebral vascular resistance (CVR) of post-mannitol infusion by group. CPP: cerebral perfusion pressure; VmMCA: velocity of middle cerebral artery.

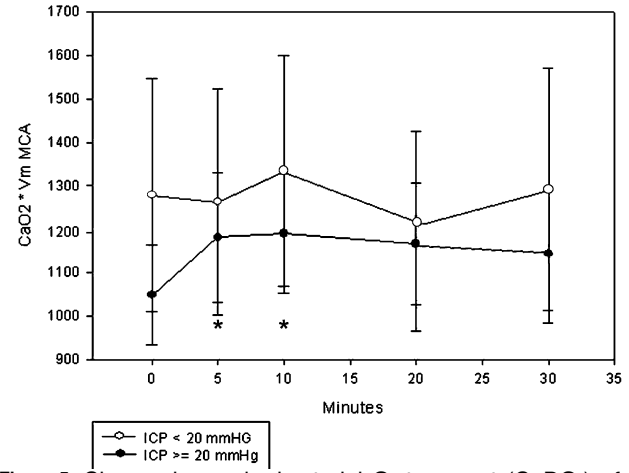

Figure 5. Change in cerebral arterial O_2 transport ($CeDO_2$) of post-mannitol infusion by group. *p < 0.05, ANOVA. CaO_2: oxygen content of cerebral artery; VmMCA: velocity of middle cerebral artery.

increase slightly but the differences were not statistically significant. While ICP was declined for 30 minutes after mannitol infusion, and the difference from baseline did not reach statistical significance at each-5 minute interval.

The MAP, CPP and CVP increased in early stage after mannitol infusion, with significant difference of CVP ($p < 0.05$), in group II and is demonstrated in Fig. 2. The CVP from baseline (mean 8.3 ± 1.3 mmHg) increased at 5-minute (mean 11.0 ± 1.2 mmHg), and 10-minute (mean 10.5 ± 1.7 mmHg), was shown statistically significant (individual $p < 0.05$). The decline of ICP lasted for 30 minutes after mannitol infusion, with statistical significance at 5-minute (value decline, 3.0 ± 1.6 mmHg) and at 10-minute (value decline, 6.5 ± 2.2 mmHg), compared to the baseline (individual $p < 0.05$). The decline of mean value in ICP was more obvious in group II than group I. Fig. 3 shows the changes in Hb and arterial oxygen content during the mannitol infusion period in both groups. The decline in Hb was statistically significant at 5- and 10-minute interval in group I ($p < 0.05$), and more significant in group II ($p < 0.01$). While CaO_2 tended to decrease in both groups, with a more statistical significance in group II during the same interval (individual $p < 0.05$) of post-mannitol infusion. The decline of CaO_2 indicated the O_2 saturation to the brain was insufficient. However, the slope resumed up after 10-minute period in order to deliver adequate O_2 to the penumbral brain. There were no differences after this period.

Plots on the mean velocity of MCA (VmMCA) by TCD monitoring reached into the peak at 10 minutes in both groups but without statistical significance within 30 minutes (Figure not shown). The change of slope was unremarkable in group I than in group II, and maintained a plateau after the peak with a relatively constant flow. Although the time to the peak varied in our patients, there was seen on a steady velocity after the initial fluctuation in all subjects.

The CVR decline lasted for 30 minutes in group II, but was not consistent in group I after mannitol infusion, as shown in Fig. 4. There were no significant differences as compared to the baseline. The decline in vascular resistance of CVR was supposed by increasing the cerebral blood flow or decreasing the ICP.

The $CeDO_2$ changes after mannitol infusion is shown in Fig. 5. The $CeDO_2$ indicated the transported ability of oxygen delivery to the brain. The $CeDO_2$ at baseline was 1048.6 ± 114.8 (ml/dl×cm/sec). It increased to $1181.5 \pm$

Table. *Time regressed to diversity variables by linear models in ICP < 20 mmHg and ICP ≧ 20 mmHg within 10 minutes after mannitol infusion*

Variables	Equation of linear regression		P value
	ICP ≥ 20mmHg	ICP < 20 mmHg	
MAP	0.94 + 0.23× time	0.51 + 0.16× time	0.040*
ICP	- 0.51 - 0.46× time	- 0.24 - 0.13× time	0.019*
CPP	0.53 + 0.27× time	0.42 + 0.70× time	0.040*
CVP	0.49 + 0.27× time	0.05 + 0.24× time	0.005*
Vm-MCA	3.18 + 1.20× time	1.55 + 1.28× time	0.018*
$CeDO_2$	21.21 + 13.86× time	14.41 + 5.51× time	0.039*

MAP: mean artery pressure; ICP: intracranial pressure; CPP: cerebral perfusion pressure; CVP: central venous pressure; Vm-MCA: mean velocity of the middle cerebral artery, $CeDO_2$: cerebral O_2 transport ability.

148.8 and 1208.3±125.5 (ml/dl×cm/sec) at 5-, and 10-minute intervals in group II with statistical significance (individual $p < 0.05$). This ability to maintain constant oxygen supply to the brain was fluctuated in group I, and had no statistical significance either.

The summary of the slopes in regression lines by 10 minutes was analyzed by checking the variables due to the most significant changes occurred in this early period (Table). These computerized complicated data demonstrated that MAP, CPP, ICP, CVP, VmMCA and $CeDO_2$ were statistically significant (all $p < 0.05$) between both groups of early post-mannitol infusion.

DISCUSSION

Although the sample size is small, our study pointed out that mannitol infusion induced early dynamic response to decline ICP and had some parametric changes in TBI patients. These changes were more obviously in patients with ICP ≥ 20 mmHg. Our results showed two stages of dynamic changes. An initial hemodilutional stage (Hb decrease, CVP increase) followed by a hemo-concentration was seen. These findings confirmed the previous reports[1-5] as a systemic and cerebral interaction, and demonstrated an osmotic effect earlier than the diuretic response after mannitol infusion. The slope decline of ICP was less sharp than those of Hb and CaO_2, which indicated that the hemodilutional effect was far beyond the vasoconstriction to the brain before diuresis occurred. These findings were consistent with the findings that early response of mannitol infusion is rather a change in the cerebral vasculature and the hemodilutional effect[12], but not due to dehydration of brain tissue[19].

Our results showed an increasing in blood flow velocity (VmMCA), CVP, O_2-transport ability ($CeDO_2$), and a decreasing in estimated cerebral resistance (CVR), CaO_2 and Hb within 10 minutes after mannitol infusion. These findings were consistent with ICP changes, and more apparent in patients with ICP ≥ 20 mmHg. It is believed that increase of cerebral blood flow and $CeDO_2$ in the early stage is to deliver sufficient O_2 to brain cells, particularly in critical patients. The constriction of vascular beds followed by a diuretic reaction is thought to be a compensatory process, and mannitol induced both effects in this process[11]. In the pharmacokinetics of mannitol infusion, the onset can happen as early as 3-15 minutes and duration lasts for 2-8 hours depending on the doses or the infusion rate[1,14]. In clinical practice, mannitol was used effectively to reduce ICP, and this effect was verified by empirical and experimental studies [5,7,11,14,21]. However, some practitioners argued its controversial effectiveness and osmotic ability[8]. We speculated that the benefit of mannitol infusion might be associated with the integrity of blood-brain barrier (BBB)[7,21].

Since BBB played a role in controlling certain substances into the brain tissues, its damage in severe TBI patients could be reflected by dys-regulation of cerebral blood flow with upstream breakthrough or extreme low velocity[16,21]. The cerebral blood flow is a product of mean velocity and cross-sectional area of the vessels, and its increase in velocity and decrease in CVR directly reveal the cerebral blood flow through the conducting arteries[20]. By the role of vasodilatation-vasoconstriction

cascade to BBB[5,21], the increase of cerebral blood flow would increase the O_2 delivery and followed by regulatory vasoconstriction in peripheral cerebral arterioles that made the intra-cerebral blood volume decrease to lower the ICP if the BBB was intact. While the BBB was breakdown (decrease in CVR and increase in VmMCA), the fluctuation of surging cerebral velocity and poor vascular compliance would cause an unstable flow pattern rather than a constant one.

Our study found that the VmMCA was increasing by 10 minutes and followed by a constant flow pattern to the end of 30 minutes. The regulation of cerebral flow occurred after the fluctuation, indicated that the BBB was preserved to a certain degree. In the literature, Muzzilaar et al.[11] have indicated that mannitol (0.66 gm/kg) decreased ICP by 27.2% at 25 minutes after mannitol infusion if the auto-regulation was intact. Conversely, mannitol infusion would decrease ICP by only 4.7% if the regulatory mechanism was damaged[21]. In our series, compared to a previous report[11], mannitol (0.5 gm/Kg) infusion decreased ICP at 25 minutes by 20.3% in group I (ICP < 20 mmHg), and by 24.6% at the same interval in group II (ICP ≥ 20 mmHg). This indicated that the regulatory ability in our patients was not fully broken, and mannitol in lowering ICP in both groups was still effective. It highlighted a fact that mannitol was useful to decline ICP during the early stage of TBI patients and could last for 30 minutes of the osmotic effect, and BBB played an important role in this effect.

In animal study using a pial window technique in cats, Muizelaar et al.[12], had shown the maximal changes in blood viscosity and in pial vessels diameters at 10 minutes of post-mannitol infusion. The pial vascular constriction occurred quickly to mannitol bolus might denote a response to an increase in preload. Furthermore, it has been suggested that vasoconstriction was greater in small arterioles (<100 um) than in large ones (>100um), and the diameters of cerebral arteries did not change. In their study, the authors found that hemodilution was associated with zero or only negative (-4.4%) decrease in diameters on the cerebral arteries. This explained the hypothesis that early hemodilution induced a decrease in cerebral resistance but had no influence on the diameters of cerebral arteries. Our results showed a non-significant decrease (2-6%) of CVR during 30 minutes in TBI patients. This reflected that cerebral vessels compliances were not changed, and by raising the possibilities, the decline in ICP was contributed to the majority of pial vessels constriction, rather than the dilatation of cerebral arteries.

The changes in MAP, CPP, ICP, CVP, VmMCA, and $CeDO_2$ were marked in patients with ICP ≥ 20 mmHg (equal to CPP < 70 mmHg) within early period after mannitol infusion by linear models (Table). The mathematic regression transform estimated the intercept and standard deviation within 10 minutes, during which period several parameters had statistically significant differences. These results revealed even small changes could have considerable difference in TBI patients with ICP ≥ 20 mmHg, which were consistent with reports that mannitol had more consequence on high ICP or low CPP patients beyond its volume effect.

Though our sample is small with a wide-range of standard deviation, the results highlighted significant findings that mannitol had cerebral effects in lowering ICP, increasing MAP, CPP, Vm-MCA, and O_2 transport ability, and systemic effects in increasing CVP and decreasing Hb and O_2 saturation in patients with ICP ≥ 20 mmHg than in patients with ICP < 20mmHg within the early stage of traumatic events.

CONCULSION

The response of mannitol infusion can happen as early as 5-10 minutes including decreasing ICP, cerebral vascular resistance, Hb, and blood O_2 contents, and increasing MAP, VmMCA, O_2 transport, and CVP. Several parameters were noted significantly different during early stage between TBI patients with ICP ≥ 20 mmHg and ICP < 20 mmHg.

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