Hemodynamic effects of mannitol infusion in patients with acute intracerebral hemorrhage[1]

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ABSTRACT

PURPOSE: To evaluate hemodynamic effects of mannitol infusion in patients with acute intracerebral hemorrhage.

METHODS: Thirty patients with acute intracerebral hemorrhage were enrolled. Transcranial doppler was used to detect variables of bilateral middle cerebral arteria (MCA) including mean velocity (Vm) and pulsitility index (PI) before and after125ml and 250ml mannitol infusion (0, 30, 60, 90, 120, 180, 240 min).

RESULTS: When 125ml or 250ml mannitol was infused in patients with acute intracerebral hemorrhage, Vm of bilateral MCA elevated, and reached the top at 30min, and then decreased. PI decreased in the affected MCA (250ml) and in the unaffected MCA (125ml and 250ml).

CONCLUSION: Mannitol infusion in patients with acute intracerebral hemorrhage can improve cerebral blood flow in bilateral hemispheres and decrease intracranial pressure in the hemorrhagic hemisphere (250ml) and in the nonhemorrhagic hemisphere (125ml and 250ml).

Key words: Cerebral Hemorrhage. Regional Blood Flow. Ultrasonography, Dopple, Transcranial. Mannitol.

Introduction

Intracerebral hemorrhage (ICH) accounts for approximately 10% to 15% of first-ever strokes, with a 30-day mortality rate of 35% to 52%[1-2]. Mannitol is effective in reversing acute brain swelling. So it has been used in the management of ICH since 1960s. American Heart Association/ American Stroke Association Stroke Council have recommended it for the management of spontaneous ICH to maintain cerebral perfusion pressure (CPP) >70 mm Hg (Class IIa, Level of Evidence B)[3]. Mannitol is also used routinely in China. There is evidence that, in prolonged dosage, mannitol may pass might cause increased intracranial pressure[4]. There is limited scientific information about its benefit, specific thresholds and the possible mechanism in ICH[5-9]. Cochrane review has shown that there is currently not enough evidence to decide whether the routine use of mannitol in acute stroke would result in any beneficial or harmful effect[10]. The present study aims at evaluating the effect of the different dosage mannitol bolus (125ml vs 250ml) on cerebral blood flow and intracranial pressure.

Methods

This trial was conducted in Department of Neurology of Xuanwu Hospital, Capital Medical University. The Xuanwu hospital Ethical Committee approved the design of the study, and written informed consent was obtained from each patient's relatives.

Patients were included if they were CT-documented supratentorial ICH, admission within 5 days of onset and age range from 40 to 90. Patients were excluded if they had any of the following criteria surgical hematoma evacuation or ventriculostomy, history of ischemic stroke or carotid stenosis, hemorrhage related to trauma, neoplasm, aneurysm, arteriovenous malformation, or coagulopathy, severely functional disorder of heart, lung, and renal, or deficient acoustic window. All the patients underwent neurological evaluation. Consciousness was evaluated by Glasgow Coma Scale. Presence of blood pressure (BP), heart ratio (HR), Pulse Oxygen Saturation (SpO_2), haematocrit (HCT) and blood gas analysis were noted. Cranial CT scan was carried out using a spiral CT scanner obtaining 10 mm axial sections parallel to orbitomeatal line. The size of hematoma was calculated as $A \times B \times C \times \Pi/6$, where A=the largest diameter of hematoma in cm, B=diameter 90º to A in cm and C=number of parenchymal hematoma seen in 1cm slice.

Treatment and examination

All patients received 20% mannitol 125ml intravenous bolus infused within 15 min. Six hours later they received 20% mannitol 250ml intravenous bolus infused within 30 min. In the six hours before the test they didn't infuse any osmotic agent.

A 2-MHz pulse-wave Doppler probe placed on the temporal window was connected to a transcranial Doppler (TCD) instrument to measure the mean, systolic, and diastolic values of flow velocity (Vm, Vs, Vd, respectively) in both middle cerebral artery before and after mannitol infusion (0, 30, 60, 90, 120, 180, 240 min). The values were recorded at the level of maximal mean velocity. The pulsatility index (PI) [(Vs -Vd)/Vm] was then calculated. Percentage[(Tn-T0)/T0×100%]was calculated to show the change of TCD value. T0 and Tn were the TCD variables before and after mannitol infusion. Systolic and diastolic blood pressures were recorded at the time of TCD examination.

Statistic analysis

Analysis was performed using the SPSS (v.11.5) software program. Continuous variables were described as median ± standard deviation. The variance analysis was applied to compare Vm and PI in the different times. The paired-samples t test was applied to compare Vm and PI in the different side and. Statistical significance was declared when $p<0.05$.

Results

Thirty patients with ICH were enrolled within 5 days of symptom onset. The characteristics of the patients are shown in Table 1.

TABLE 1 - Demographic data (mean ± SD) of the patients (n=30).

Demographic data		
Age, yrs		58±13
Men, n		23
ICH locations, n	thalamus	10
	basal ganglia	14
	lobar	4
	basal ganglia and lobar	2
ICH volume, ml		22±12
Presumed etiologies, n	hypertension	26
	cerebral amyloid angiopathy	4

ICH: Intracerebral Hemorrhage.

Eight of them were older then 65. Ten patients' ICH volume was larger than 25ml.Systemic variables at the reference time of the patients are shown in Table 2.

TABLE 2 - Physiological data (mean ± SD) at the reference time (T0) of the patients (n=30).

Physiological data		
GCS score		14±2
HCT, %		43.96±4.70
Blood gas analysis	PH	7.41±0.02
	PaO_2, mmHg	109.21±2.87
	$PaCO_2$, mmHg	40.11±5.49
MABP, mmHg		115±16
HR, beats/minute		76±16
SpO_2, %		98.2±1.2

GCS: Glasgow Coma Scale; HCT: Haematocrit; MABP: Mean Arterial Blood Pressure; HR: Heart Rate; SpO_2: pulse oxygen saturation.

MABP, HR and SpO_2 remained unchanged during the study period. TCD variables are shown in Tables 3 and 4.

TABLE 3 - Comparison of TCD variables and percentage before and after 125ml mannitol infusion.

group		0min	30 min	60 min	90 min	120 min	180 min	240 min
affected MCA	Vm (cm/s)	52±15	58±17[b]	55±16[b]	54±16[a]	54±16[a]	52±15	54±15[a]
	Vm%	0	13.5±8.4	6.9±10.8	4.5±10.5	4.2±9.2	1.9±8.6	4.8±9.4
	PI	1.08±0.27	1.03±0.25	1.05±0.28	1.05±0.28	1.05±0.29	1.09±0.29	1.08±0.30
	PI%	0	-2.24±11.28	-0.83±10.77	-0.68±9.86	-1.43±10.24	2.35±10.38	1.00±9.54
unaffected MCA	Vm	49±11	56±13[b]	54±14[b]	51±14[a]	52±14[a]	52±12[a]	50±13
	Vm%	0	15.5±12.4	9.4±11.6	4.4±11.9	4.9±11.2	6.0±10.0	2.9±10.0
	PI	1.10±0.29	1.06±0.29[a]	1.06±0.31[b]	1.06±0.29[a]	1.06±0.30[b]	1.09±0.27	1.12±0.32
	PI%	0	-4.20±9.56	-4.75±8.72	-4.10±9.22	-4.86±7.83	-0.87±7.91	0.91±9.34

[a] $p<0.05$ vs baseline values at time 0, [b] $p<0.01$ vs baseline values at time 0.

TABLE 4 - Comparison of TCD value and percentage before and after 250ml mannitol infusion.

group		0min	30 min	60 min	90 min	120 min	180 min	240 min
affected MCA	Vm (cm/s)	52±16	62±18[b]	59±18[b]	56±18[b]	54±15	53±16	53±16
	Vm%	0	19.1±9.2	13.4±10.4	7. 8±8.3	4.7±9.4	1.9±9.4	2.4±9.6
	PI	1.08±0.27	1.00±0.23[b]	1.02±0.24[b]	1.04±0.24[a]	1.04±0.26[a]	1.08±0.27	1.05±0.23
	PI%	0	-6.31±11.53	-5.40±8.79	-2.84±10.06	-3.51±10.18	-0.37±10.07	-1.90±8.81
unaffected MCA	Vm	50±12	60±17[b]	57±15[b]	54±12[b]	53±13[b]	51±13	51±13
	Vm%	0	18.9±13.3	14.9±12.2	8.8±9.5	6.2±9.6	2.7±8.4	2. 6±9.5
	PI	1.10±0.3	1.06±0.24[c]	1.04±0.28[a]	1.05±0.28[a]	1.04±0.26[a]	1.08±0.27	1.08±0.25
	PI%	0	-2.11±11.60	-4.30±13.80	-3.23±9.71	-4.42±8.07	-0.51±10.63	-0.40±10.42

[a] $p<0.05$ vs baseline values at time 0, [b] $p<0.01$ vs baseline values at time 0, [c] $p<0.05$ the affected MCA vs the unaffected MCA.

After 125 ml mannitol infusion, Vm in the affected MCA elevated significantly from 30min to 120min, and then decreased. At 240 min Vm in the affected MCA was still higher, and Vm in the unaffected MCA elevated significantly from 30 min to 180 min, then decreased. PI in the affected MCA decreased and then elevated without significant difference. PI in the unaffected MCA decreased significantly from 30 min to 120 min than elevated. After 250 ml mannitol infusion Vm in the affected MCA elevated significantly from 30 min to 90 min, then decreased. And Vm in unaffected MCA elevated significantly from 30 min to 120min, then decreased. PI in the affected MCA decreased significantly from 30 min to 120 min then elevated. PI in the unaffected MCA decreased significantly from 60 min to 120 min then elevated.

Percentage showed the change of Vm and PI straightly. Figures 1 and 2 showed the tendency of Vm% and PI%.

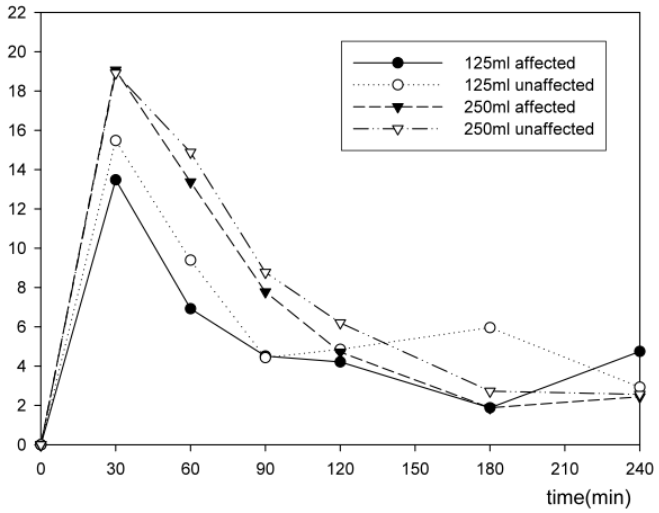

FIGURE 1 - Time-course evolution of Vm% (mean) during the 240-min period in 30 patients.

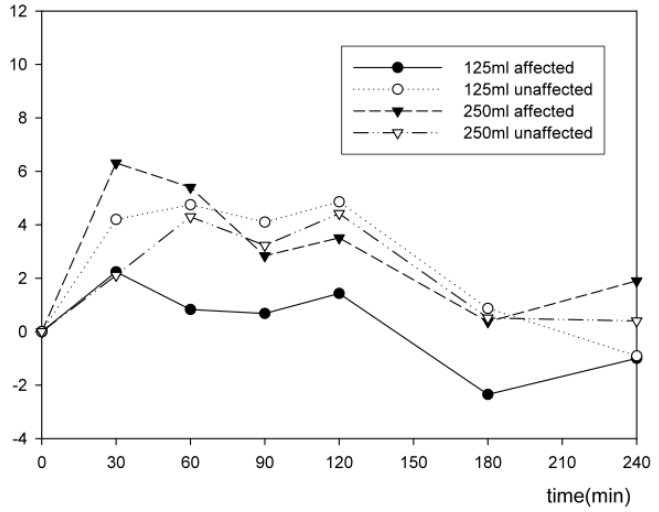

FIGURE 2 - Time-course evolution of PI% (mean) during the 240-min period in 30 patients.

After 125 ml mannitol infusion Vm% in bilateral MCA and PI% in the affected MCA reached the top at 30min. PI% in the unaffected MCA reached the top at 30 min and persist to 120 min. After 250 ml mannitol infusion Vm% in bilateral MCA and PI% in affected MCA reached the top at 30min. PI% in unaffected MCA reached the top at 60 min and persist to 120 min. The difference of Vm% in the affected MCA caused by 125 ml and 250 ml mannitol infusion existed from 30 min to 60 min. The difference of PI% between 125 ml and 250 ml mannitol infusion were not significantly.

Discussion

It is important to control intracerebral pressure (ICP) and improve CPP in patients with acute ICH. TCD is a non-invasive method for monitoring cerebral blood flow (CBF) and ICP. It has been shown to reflect both global and focal changes in ICP. Vm and PI of MCA are important indicators for monitoring. A significant correlation was found between the ICP and the PI and between the CPP and PI (the correlation coefficient of 0.938, -0.493 respectively)[11-12]. In our research PI in bilateral MCA before 125ml or 250ml mannitol infusion didn't elevate significantly. It meant that ICP increased limitedly in our patients. One reason was that majority of our patients had medium or small size hematoma(21.94±12.18 cm^3). Anther was that some patients were older so they had some compensation space for their hematoma. Our study showed that PI decreased just in unaffected MCA after 125ml mannitol infusion and in bilateral MCA after 250ml mannitol infusion. It suggests that 125ml mannitol decrease ICP in the uneffected hemisphere and 250ml mannitol decrease ICP in bilateral hemispheres. 250ml mannitol is more powerful in lower ICP than 125ml.

Vm of MCA is another important indicator. This study showed that mannitol infusion increased Vm of MCA significantly from 30min to 120min. The changes of Vm agreed with other studies[13-14]. The mechanisms that mannitol increased cerebral flow velocity include: increasing blood volume, decreasing ICP ,decreasing blood viscosity, increasing erythrocyte flexibility and dilating arteriole by non- nitric oxide -dependence mechanism. There is growing evidence that the region surrounding the hematoma is hypoperfusion[15-17] which appeared to be time dependent and correlated with the size of hematomas[18,19]. The persistence of hypoperfusion correlated with a poor clinical outcome by day 90 and the therapeutic interventions could increase the volume of recovered perfusion[19,20]. Our study showed that Vm increased after different dosage mannitol infusion. It maybe helpful to improve perfusion surrounding the hemorrhage, to decrease injure caused

by hypoperfusion and to promote neurological functional recovery. The difference of Vm% caused by 125ml and 250ml mannitol infusion existed from 30min to 60min. 250ml mannitol was more powerful in increasing flow velocity. So just considering effect of one dosage mannitol, 250ml was more powerful in decreaseing ICP and improving CBF.

Our result showed that there wasn't significantly difference between bilateral Vm and between bilateral PI. It didn't agree with the traditional opinion that mannitol therapy was attributed to shrinkage of the normal hemisphere rather than the side with stroke, which resulted in aggravation of midline shift[21]. In our study one dosage mannitol (125 ml or 250 ml) infusion didn't cause pressure imbalance. Mayer study compared the difference TCD value in different size hematoma. Their result was that asymmetry of intracranial hemodynamics occurs when intracerebral hemorrhage volumes exceed 25 ml. Compared with patients with small hemorrhages, those with large hemorrhages had significantly higher affected PI (1.72 versus 1.13, P<.0001) [22]. According to their method, we also divided our patients to two groups. But there wasn't different in Vm or PI before mannitol infusion between two groups. We thought the reason was that both study were small sample, so more study was required.

Our study has some limitations. We focused on one dosage mannitol effect. How this hemadynamics change work on the long term prognosis is unknown. Further studies are required about the effect of mannitol on survival rate, disability rate, quality of life and their relationship with hemadynamic changes.

Conclusion

Mannitol infusion in patients with acute intracerebral hemorrhage can improve cerebral blood flow in bilateral hemispheres and decrease intracranial pressure in the hemorrhagic hemisphere (250ml) and in the nonhemorrhagic hemisphere (125ml and 250ml).

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