Effects of Hypertonic (10%) Saline in Patients With Raised Intracranial Pressure After Stroke

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Effects of Hypertonic (10%) Saline in Patients With Raised Intracranial Pressure After Stroke

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Background and Purpose—The aim of this study was to evaluate the effects of hypertonic saline in stroke patients with increased intracranial pressure (ICP) after conventional therapy with mannitol had failed.

Methods—Twenty-two episodes of ICP crisis occurred in 8 patients in whom the standard treatment of 200 mL of 20% mannitol was not effective. ICP crisis was defined as an increase in ICP of 20 mm Hg (n=18), pupillary abnormality (n=3), or a combination of both (n=1). The patients were treated with 75 mL of 10% saline over the course of 15 minutes. ICP, mean arterial blood pressure, and cerebral perfusion pressure were monitored for 4 hours. Blood gases, hematocrit, hemoglobin, pH, osmolarity, and electrolytes levels were measured before and 15 and 60 minutes after the start of infusion. Treatment was regarded as effective if ICP decreased >10% or the pupillary reaction had normalized.

Results—Treatment was effective in all 22 episodes. The maximum ICP decrease was 9.9 mm Hg 35 minutes after the start of infusion. Thereafter, ICP began to rise again. There was no constant effect on mean arterial blood pressure, whereas cerebral perfusion pressure was consistently increased. Blood osmolarity rose by 9 mmol/L and serum sodium by 5.6 mmol/L. Potassium levels, hemoglobin, hematocrit, and pH were slightly decreased. No unexpected side effects were noted.

Conclusions—Infusion of 75 mL hypertonic (10%) saline decreases elevated ICP and increases cerebral perfusion pressure in stroke patients in whom mannitol had failed. The effect on the ICP and cerebral perfusion pressure reaches its maximum after the end of infusion and is seen for 4 hours. **(*Stroke*. 2002;33:136-140.)**

Key Words: brain edema ■ hypertonic solution, saline ■ intracranial pressure ■ stroke

Within the first few days after hemispheric stroke, the extent and location of space-occupying brain edema, which leads to intracranial hypertension, brain tissue shifts, and tentorial herniation, are the main causes of death.[1] Over the years, some of the traditional treatment options such as barbiturates or hyperventilation have lost their shine because it has been recognized that these therapies may critically reduce cerebral perfusion pressure (CPP) and may even cause secondary ischemic damage.[2,3] In this context, hypertonic solutions offer an attractive alternative because they decrease elevated intracranial pressure (ICP) without negative effects on the CPP. Several hypertonic substances have been used, most extensively mannitol. Although large randomized trials have not yet been undertaken, various clinical and experimental studies demonstrated that single doses of mannitol reduce, at least transiently, elevated ICP.[4–8] However, there are some aspects that dampen the enthusiasm about mannitol for stroke patients. First, almost all large clinical studies with mannitol have been performed in patients with head injuries; comparable studies in stroke patients have not been undertaken. Second, the long-term beneficial effects of mannitol are unknown. Third, there is some evidence that repeated doses of mannitol may even aggravate brain edema.[9,10] Furthermore, mannitol fails to be effective in some patients, especially after repeated doses. Therefore, alternative therapies for increased ICP are warranted.

Hypertonic saline solutions were originally used for "small-volume resuscitation" in patients with hemorrhagic shock. Compared with standard shock therapy, small-volume resuscitation produces a more rapid volume expansion; increases cardiac output, systemic blood pressure, and microvascular perfusion; and may improve survival.[11,12] In the last few years, evidence has accumulated from case series and small randomized trials that hypertonic saline may be an effective treatment for brain edema and elevated ICP after head trauma.[13–20] In patients with stroke, hypertonic saline preparations have been investigated only anecdotally.[14,21,22] In a small prospective case series, Qureshi et al[14] could not detect any beneficial effect of continuous infusion of 3% saline/acetate in 14 patients who had suffered massive stroke. In a previous small randomized study, the effects of bolus infusions of mannitol and hypertonic (7.5%) saline hydroxyethyl starch solution (HS-HES) in stroke patients with acutely raised ICP were compared. Infusion of both substances markedly decreased raised ICP.[8] However, in this study, hydroxyethyl starch was added to the hypertonic saline to

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augment the action of hypertonic saline, thus leaving the role of hypertonic saline alone undetermined.

The aim of this prospective case series was to evaluate the effects of bolus infusions of hypertonic saline without the addition of any augmentative substance in patients with acutely raised ICP after conventional therapy with mannitol failed.

Materials and Methods

From January to July 2001, 8 consecutive patients with elevated ICP after acute space-occupying hemispheric stroke (n=6) or supratentorial hemorrhage with massive perifocal edema (n=2) were included in this study. All patients were treated in the neurocritical care unit according to an institutional protocol for stroke patients with elevated ICP. All patients were intubated, ventilated, and anesthetized with analgesics and sedatives. The patients were nursed in a 30° upright position. Ventilation parameters were adjusted to achieve normocapnia and a Pa_{O_2} >90 mm Hg. The ICP was continuously monitored with an intraparenchymatous (n=6) ICP device (Spiegelberg) ipsilateral to the lesion or via a ventricular catheter (n=2). ICP, pulse oxygenation, heart rate, and mean arterial blood pressure (MAP) were continuously monitored. Crystalline fluids and colloidal (hydroxyethyl starch) solutions were administered to achieve a central venous pressure of 12 to 16 cm H_2O. If volume substitution was not sufficient to reach a CPP of ≥70 mm Hg, we administered norepinephrine and/or dobutamine as a continuous infusion via a central line. Patients with large space-occupying hemispheric infarctions were treated with decompressive hemicraniectomy or therapeutic hypothermia as previously described.[23,24] Other specific therapeutic measures were not used until the ICP reached 20 mm Hg or clinical signs of markedly increased ICP were evident. As standard therapy, these patients were first treated with 200 mL of a 20% mannitol solution.

We administered hypertonic saline if standard therapy with mannitol had no or only limited, short-lasting effects and 1 or 2 of the following criteria were met: (1) spontaneous ICP elevation >20 mm Hg persisting for >5 minutes or (2) a newly observed unilateral or bilateral pupillary enlargement. Then, 75 mL of a 10% saline solution (3422 mOsm/L) was administered via a central venous catheter over a period of 15 minutes. Efficacy of this treatment was assessed 10 minutes after the end of infusion (ie, 25 minutes after start). Therapy was classified as successful if the ICP fell >10% baseline value or pupillary reaction had normalized (in patients with a pupillary abnormality). Patients in whom therapy with hypertonic saline was not successful were immediately treated with THAM-buffer solution, short-term hyperventilation, or barbiturates. Therapy with hypertonic saline could be repeated in the same patient if the first treatment had been successful and criteria for intervention were met again.

The following parameters were assessed at baseline and after 5, 10, 15 (end of infusion), 25, 35, 45, 60, 120, 180, and 240 minutes: ICP, MAP, CPP, and pupillary reaction. Pupillary reaction was categorized as normal, unilaterally abnormal (enlarged or areactive), or bilaterally abnormal. Blood osmolarity; sodium, potassium, and chloride levels; Pa_{CO_2}; Pa_{O_2}; hematocrit; hemoglobin; and pH were determined at baseline, after 15 minutes (end of infusion), and after 60 minutes.

During the first 60 minutes, ventilation parameters and concomitant medication—in particular, the rate of epinephrine infusion or additional volume replacement—were maintained, and nursing procedures such as turning or endotracheal suction were restricted to a minimum. Patients in whom the ventilation parameters or vasopressor therapy had to be modified during the first 60 minutes after infusion of hypertonic saline were excluded from further analysis. General exclusion criteria for treatment with hypertonic saline were oliguric renal failure, pulmonary edema, and cardiac failure. Hypertonic saline was not administered if baseline sodium levels were >150 mmol/L. Patient outcome was assessed 2 weeks after admission with the Glasgow outcome scale (GOS).[25]

This study was conducted according to local ethics committee standards. Informed consent was obtained from the patient's relatives. All data analysis was performed without patient identification.

Statistical analysis was performed with the Wilcoxon signed-rank test to detect differences between each time point and baseline values. Differences were considered significant at values of $P<0.05$. Data are presented as mean±SD. Statistical analysis was performed for values obtained within the first 60 minutes only, because we could not maintain possible influencing factors such as nursing procedures, ventilation parameters, or other medication for a longer period of time.

Results

In all, 22 events were treated in 8 patients (4 women; mean age, 59.8±8.8 years). Of the 6 patients with large hemispheric infarcts, 2 underwent decompressive surgery; the remaining 4 patients with large hemispheric infarcts were treated with therapeutic mild to moderate hypothermia. The mean interval between stroke onset and the first administration of hypertonic saline was 69 hours (range, 38 to 109 hours.). In those patients treated with hypothermia, ICP crises occurred almost exclusively during or shortly after rewarming.

Indications for therapy with hypertonic saline were (1) a rise in the ICP >20 mm Hg in 18 episodes, (2) newly observed pupillary abnormality in 3 episodes, and (3) ICP crisis plus pupillary abnormality in the remaining 1 episode. Precedent standard therapy with mannitol had no effect at all in 1 patient and yielded only insufficient and short-lasting effects in the other 7 patients. Concomitant therapy included continuous infusion of vasopressor drugs during the observation period in 18 episodes.

By the end of the study, 4 patients had died of uncontrollable intracranial hypertension (GOS 5). The remaining 4 patients remained severely disabled (GOS 3).

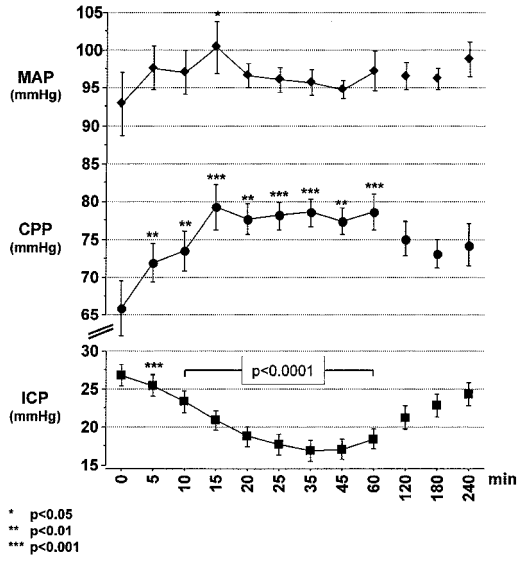
Therapy was classified as successful 10 minutes after end of infusion in all episodes.

ICP, MAP, and CPP are presented in the Figure. Mean baseline ICP was 26.7±6.8 mm Hg. Immediately after the start of mannitol infusion, ICP fell significantly ($P<0.001$ for all time points). After 15 minutes, at the end of infusion, ICP dropped by 22% to 20.8±6.1 mm Hg. The highest drop in ICP from baseline level, 38%, occurred after 35 minutes (to 16.8±6.5 mm Hg, $P<0.0001$).

The initial MAP was 92.4±19.3 mm Hg and remained unchanged except for the time point at the end of infusion (mean increase of 8.0% to 99.8±16.2 mm Hg, $P<0.05$).

Mainly as an effect of the changes in ICP, CPP was significantly higher than at baseline at all time points. The initial CPP was 65.7±17.4 mm Hg. The increase in CPP was most marked after 15 minutes at the end of infusion (mean increase of 20.2% to 79.0±14.2mm Hg, $P<0.001$).

Arterial blood gases, pH, osmolarity, serum electrolytes, and hematocrit/hemoglobin are given in the Table. At the end of infusion, hematocrit levels and hemoglobin had decreased. Subsequently, hemoglobin levels rose again but were still below baseline after 60 minutes. Both serum sodium and chloride levels increased by 5.6 mmol/L after 15 minutes. Serum sodium and chloride decreased thereafter but still remained elevated after 60 minutes.



ICP, CPP, and MAP of 22 episodes of increased ICP after stroke. After the start of infusion of 75 mL of 10% saline, ICP fell significantly and CPP increased, mainly because of the decrease in ICP. Except for 1 time point at the end of infusion after 15 minutes, MAP remained unchanged. Maximum reduction in ICP occurred after 35 minutes, 20 minutes after the end of infusion. Thereafter, ICP rose again bud did not reach baseline values throughout the observation period. Statistical analysis was performed for values obtained within the first 60 minutes only, because possible influencing factors such as nursing procedures, ventilation parameters, or other medication could not maintained unchanged for a longer period of time. All data are presented as mean±SE.

Blood osmolarity rose by 9 mOsm/L at the end of infusion. After that time point, osmolarity fell again; however, after 60 minutes, osmolarity was still higher than at baseline.

The pH fell slightly as a result of hyperchloremic acidosis. In addition, there was a slight decrease in potassium levels.

Pa_{O_2} and Pa_{CO_2} remained unchanged during the observation period. We did not notice any side effect or, in particular, any sign of cardiovascular or pulmonary decompensation.

Repeated interventions became necessary in all but 1 patient (mean, 2.8 events per patient; range, 1 to 4). Because of the small number of repeated events, further analysis of the effects of repeated interventions was not performed.

Discussion

In this study, bolus infusion of hypertonic saline consistently led to an almost immediate and substantial decrease in an acutely raised ICP and to a marked rise in CPP, mirroring the effects on ICP. In all patients, previous treatment with mannitol was not effective. It is particularly remarkable that the infusion of hypertonic saline was highly effective, although the osmolarity was markedly increased already before start of treatment with hypertonic saline by previous therapy with mannitol. The osmolar load of 75 mL of 10% saline (3422 mOsm/L) is comparable to that of 200 mL of 20% mannitol (1100 mOsm/L). One may speculate that the repeated administration of mannitol could have evoked the same effects, but in this emergency situation with acutely elevated ICP, we did not consider it reasonable to repeat a treatment that initially was not successful. The osmotic effect of hypertonic saline may be more pronounced than with equiosmolar amounts of mannitol, because, despite the much higher molecular weight of sodium, the blood-brain barrier permeability is lower for sodium.[13] The volume of hypertonic saline is smaller than that of mannitol; however, the total volume of both preparations is so small that this difference probably has no clinical relevance. Mannitol acts as a potent diuretic drug. Hypertonic saline also has a 2-fold diuretic effect: directly as a consequence of natriuresis and indirectly via the release of atrial natriuretic hormone.[13] A further advantage of hypertonic saline over mannitol is its very low price. Infusion of hypertonic saline may also carry some risks, however. Rapid changes in serum sodium concentrations may result in seizures and are associated with central pontine myelinolysis, although this seems to occur predominantly in chronic states of hyponatremia. Until now, there have been no reports of central pontine myelinolysis after administration of hypertonic saline. Other possible complications of treatment with hypertonic solutions in general such as heart failure, lung edema, hemolysis, and coagulation abnormalities were not noted in our patients. After prolonged use of hypertonic solutions, hyperchloremic acidosis will develop. In our patients, pH fell significantly after administration of hypertonic saline, but the degree of change was quite small and probably clinically not relevant. To prevent hyperchloremic acidosis, hypertonic saline/acetate solutions have been

Blood Osmolarity, Blood Electrolytes, Arterial Blood Gases, pH, and Hematocrit at Baseline and at 15 Minutes (End of Infusion) and 60 Minutes After Start of Infusion

		At 15 min		At 60 min	
	Baseline	Value	*P*	Value	*P*
Osmolarity, mOsm/L	343±16	352±16	<0.0001	346±16	0.0002
Na^+, mmol/L	144.1±4.7	149.7±5.1	<0.0001	146.5±5.0	0.0002
K^+, mmol/L	4.2±0.4	4.0±0.4	<0.0001	4.2±0.4	0.87
Cl^-, mmol/L	115.0±4.9	120.6±5.4	<0.0001	118.5±5.0	<0.0001
pH	7.406±0.056	7.406±0.052	0.02	7.410±0.052	0.06
Hematocrit, %	33.5±4.6	33.2±4.1	0.0003	33.7±4.3	0.19
Hemoglobin, g/dL	11.5±1.6	11.0±1.5	<0.0001	11.3±1.6	<0.0001
Pa_{O_2}, mm Hg	104±13	105±12	0.42	105±11	0.68
Pa_{CO_2}, mm Hg	40±2	40±1	0.65	40±1	0.98

used in patients continuously treated with hypertonic saline.[14] This is probably not necessary if hypertonic saline is administered as a bolus infusion. However, repeated use of hypertonic saline will be limited by hypernatremia, which inevitably occurs after multiple treatments. In contrast, mannitol leads to hyponatremia. Because of its complementary effects on sodium levels, which may limit the repeated use of either drug, mannitol and hypertonic saline could be used in alternation if repeated treatments are needed.

It has been proposed that repeated infusions of mannitol could aggravate cerebral edema if the osmotic substances migrate through a damaged blood-brain barrier into the brain tissue, reversing the osmotic gradient.[9] It seems unlikely that a damaged blood-brain barrier would maintain its selective permeability; therefore, this presumed negative effect would probably occur with hypertonic saline also. Furthermore, osmotic agents predominantly lead to dehydration and shrinkage of normal brain tissue and may facilitate displacement of brain tissue and even increase the risk of herniation.[26] However, to date, these largely theoretical considerations could not be convincingly substantiated in clinical studies. In 2 single patients, edema formation late in the course of intracerebral hemorrhage has been linked to prolonged administration of hypertonic saline,[22] but it must be noted that late edema formation frequently occurs in this patient group regardless of therapeutic measures.

In our euvolemic patients, arterial blood pressure did not persistently change after infusion of hypertonic saline. This result is in agreement with other clinical and experimental studies that have shown that in contrast to patients with hemorrhagic shock, the blood pressure remains unaffected or even decreases after hypertonic saline, probably because of a reactive decrease in the peripheral resistance.[21,27,28]

In a previous study, we evaluated the effects of hypertonic saline combined with HS-HES compared with standard treatment with mannitol.[8] Although the results of the 2 studies can be compared only with great caution, inclusion criteria and treatment modalities were nearly identical (7.5 g sodium chloride was infused over 15 minutes in both studies). The previously described effects of HS-HES on laboratory parameters, ICP, and MAP were nearly identical to those obtained in the present study using hypertonic saline alone. The effect mechanisms of HS-HES are complex, because it consists of 2 components: sodium chloride, which is responsible primarily for the osmotic gradient, and HES, which is added to maintain the short-living volume effect of hypertonic saline. To improve the cerebral microcirculation, HES or dextrans have been used for many years in stroke but have failed to improve patient outcome.[29] To date, a clear advantage of the augmentative addition of colloids to hypertonic saline over hypertonic saline alone has not been demonstrated in various animal or clinical studies (for a review, see reference 13). We recommend that colloids not be used in addition to hypertonic saline until more evidence has been collected supporting this treatment strategy.

In this study, we assessed the early effects of hypertonic saline. It appears to be indisputable that hypertonic saline can, at least transiently, decrease an elevated ICP and therefore may be beneficial in emergency situations in an acutely deteriorating patient before therapies such as hematoma evacuation or decompressive surgery can be initiated. The long-term effects of repeated or continuous treatments with hypertonic saline in stroke patients remain unclear. In a mixed patient population with various intracranial pathological conditions leading to brain edema, continuous hypertonic (3%) saline/acetate failed to show any beneficial effect on lateral displacement of the brain and other outcome measures in those patients with ischemic and hemorrhagic stroke.[14]

Our results strongly indicate that hypertonic saline can be successfully used in patients with acutely raised ICP after stroke, even after conventional treatment with mannitol has failed. The optimal concentration and dosage, duration and mode of therapy, and in particular long-term safety and efficacy of this treatment need to be evaluated further. However, although hypertonic saline certainly is no magic bullet for the treatment of brain edema, our results suggest that hypertonic saline is at least a useful alternative to current therapies of brain edema after stroke.

Conclusions

Single doses of 75 mL hypertonic (10%) saline reduce elevated ICP and augment CPP in patients with brain edema after stroke after standard therapy with mannitol has failed, even if the osmolarity is already increased by previous treatments with mannitol. Hypertonic saline has no major effect on MAP. The effects on ICP and CPP are most prominent shortly after administration but are seen over 4 hours. Unexpected side effects were not noted. Hypertonic saline can be successfully used after mannitol has failed.

References

1. Hacke W, Schwab S, Horn M, Spranger M, De Georgia M, von Kummer R. “Malignant” middle cerebral artery territory infarction: clinical course and prognostic signs. *Arch Neurol*. 1996;53:309–315.
2. Muizelaar JP, Marmarou A, Ward JD, Kontos HA, Choi SC, Becker DP, Gruemer H, Young HF. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. *J Neurosurg*. 1991;75:731–739.
3. Schwab S, Spranger M, Schwarz S, Hacke W. Barbiturate coma in severe hemispheric stroke: useful or obsolete? *Neurology* 1997;48:1608–1613.
4. Marshall LF, RW SM, Rauscher LA, Shapiro HM. Mannitol dose requirements in brain-injured patients. *J Neurosurg*. 1978;48:169–172.
5. Muizelaar JP, Lutz HA 3rd, Becker DP. Effect of mannitol on ICP and CBF and correlation with pressure autoregulation in severely head-injured patients. *J Neurosurg*. 1984;61:700–706.
6. Kirkpatrick PJ, Smielewski P, Piechnik S, Pickard JD, Czosnyka M. Early effects of mannitol in patients with head injuries assessed using bedside multimodality monitoring. *Neurosurgery* 1996;39:714–720; discussion 720–721.
7. Biestro A, Alberti R, Galli R, Cancela M, Soca A, Panzardo H, Borovich B. Osmotherapy for increased intracranial pressure: comparison between mannitol and glycerol. *Acta Neurochir (Wien)*. 1997;139:725–732.
8. Schwarz S, Schwab S, Bertram M, Aschoff A, Hacke W. Effects of hypertonic saline hydroxyethyl starch solution and mannitol in patients with increased intracranial pressure after stroke. *Stroke*. 1998;29:1550–1555.
9. Kaufmann AM, Cardoso ER. Aggravation of vasogenic cerebral edema by multiple-dose mannitol. *J Neurosurg*. 1992;77:584–589.
10. Bereczki D, Liu M, Prado GF, Fekete I. Cochrane report: A systematic review of mannitol therapy for acute ischemic stroke and cerebral parenchymal hemorrhage. *Stroke*. 2000;31:2719–2722.
11. Vassar MJ, Fischer RP, O’Brien PE, Bachulis BL, Chambers JA, Hoyt DB, Holcroft JW. A multicenter trial for resuscitation of injured patients with 7.5% sodium chloride: the effect of added dextran 70. *Arch Surg*. 1993;128:1003–1013.

12. Kramer GC, Perron PR, Lindsay DC, Ho HS, Gunther RA, Boyle WA, Holcroft JW. Small-volume resuscitation with hypertonic saline dextran solution. *Surgery*. 1986;100:239–247.
13. Qureshi AI, Suarez JI. Use of hypertonic saline solutions in treatment of cerebral edema and intracranial hypertension. *Crit Care Med*. 2000;28: 3301–3313.
14. Qureshi AI, Suarez JI, Bhardwaj A, Mirski M, Schnitzer MS, Hanley DF, Ulatowski JA. Use of hypertonic (3%) saline/acetate infusion in the treatment of cerebral edema: Effect on intracranial pressure and lateral displacement of the brain. *Crit Care Med*. 1998;26:440–446.
15. Schatzmann C, Heissler HE, Konig K, Klinge-Xhemajli P, Rickels E, Muhling M, Borschel M. Treatment of elevated intracranial pressure by infusions of 10% saline in severely head injured patients. *Acta Neurochir Suppl (Wien)*. 1998;71:31–33.
16. Simma B, Burger R, Falk M, Sacher P, Fanconi S. A prospective, randomized, and controlled study of fluid management in children with severe head injury: lactated Ringer's solution versus hypertonic saline. *Crit Care Med*. 1998;26:1265–1270.
17. Shackford SR, Bourguignon PR, Wald SL, Rogers FB, Osler TM, Clark DE. Hypertonic saline resuscitation of patients with head injury: a prospective, randomized clinical trial. *J Trauma*. 1998;44:50–58.
18. Peterson B, Khanna S, Fisher B, Marshall L. Prolonged hypernatremia controls elevated intracranial pressure in head-injured pediatric patients. *Crit Care Med*. 2000;28:1136–1143.
19. Horn P, Munch E, Vajkoczy P, Herrmann P, Quintel M, Schilling L, Schmiedek P, Schurer L. Hypertonic saline solution for control of elevated intracranial pressure in patients with exhausted response to mannitol and barbiturates. *Neurol Res*. 1999;21:758–764.
20. Khanna S, Davis D, Peterson B, Fisher B, Tung H, O'Quigley J, Deutsch R. Use of hypertonic saline in the treatment of severe refractory posttraumatic intracranial hypertension in pediatric traumatic brain injury. *Crit Care Med*. 2000;28:1144–1151.
21. Suarez JI, Qureshi AI, Bhardwaj A, Williams MA, Schnitzer MS, Mirski M, Hanley DF, Ulatowski JA. Treatment of refractory intracranial hypertension with 23.4% saline. *Crit Care Med*. 1998;26:1118–1122.
22. Qureshi AI, Suarez JI, Bhardwaj A. Malignant cerebral edema in patients with hypertensive intracerebral hemorrhage associated with hypertonic saline infusion: a rebound phenomenon? *J Neurosurg Anesthesiol*. 1998; 10:188–192.
23. Schwab S, Schwarz S, Spranger M, Keller E, Bertram M, Hacke W. Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction. *Stroke*. 1998;29:2461–2466.
24. Schwab S, Steiner T, Aschoff A, Schwarz S, Steiner HH, Jansen O, Hacke W. Early hemicraniectomy in patients with complete middle cerebral artery infarction. *Stroke*. 1998;29:1888–1893.
25. Jennett B, Bond M. Assessment of outcome after severe brain damage: a practical scale. *Lancet*. 1975;1:480–484.
26. Frank JI. Large hemispheric infarction, deterioration, and intracranial pressure. *Neurology*. 1995;45:1286–1290.
27. Dubick MA, Davis JM, Myers T, Wade CE, Kramer GC. Dose response effects of hypertonic saline and dextran on cardiovascular responses and plasma volume expansion in sheep. *Shock*. 1995;3:137–144.
28. Hartl R, Ghajar J, Hochleuthner H, Mauritz W. Treatment of refractory intracranial hypertension in severe traumatic brain injury with repetitive hypertonic/hyperoncotic infusions. *Zentralbl Chir*. 1997;122:181–185.
29. Italian Acute Stroke Study Group. Haemodilution in acute stroke: results of the Italian hemodilution trial. *Lancet*. 1988;1:318–320.