NOTE *Internal Medicine*

The Effect of 7.2% Hypertonic Saline Solution on the Duration of Sodium Gradient between the Cerebrospinal Fluid and the Venous Circulation in the Dog

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ABSTRACT. To determine the duration of water movement from cerebrospinal fluid (CSF) into venous blood by the infusion of 7.2% hypertonic saline solution (HSS), the sodium gradient between venous blood and CSF were examined. Venous sodium concentrations remained higher than that in CSF for duration of 60 min following HSS infusion. By 90 min, the CSF sodium concentration reached the equilibrium with venous sodium concentration. Those data suggests that the duration of time during which water moved from CSF into capillaries in brain by the gradient of sodium concentration was less than 90 min.

KEY WORDS: canine, cerebrospinal fluid, hypertonic saline solution.

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Intravenous (IV) infusion of a small volume (3–5 m*l*/kg) of 7.2%-hypertonic saline solution (HSS: 2,400 mOsm/kg•H_2O) has been successfully used to resuscitate dogs with experimental hemorrhage [9, 18, 21]. The infusion of HSS causes increase in plasma volume because the hypertonicity of this solution promotes water redistribution from interstitial and intracellular fluid compartments [7]. The infusion of HSS in animal models of hemorrhagic- or endotoxic-shock improved cardiac output, cardiac index, myocardial stroke work efficiency [2, 10, 16] and oxygen delivery [17]. Small volume HSS infusion also restored mean arterial pressure (MAP) and reduced peripheral and pulmonary vascular resistance [2, 10, 16]. For these reasons, small volumes of HSS have been effectively used in resuscitation from shock in the dog [8].

The effect of HSS on intracranial pressure (ICP) has been also discussed widely. ICP was lower in dogs with hemorrhagic shock when they were resuscitated with HSS than that in those resuscitated with lactated Ringer's solution [13]. In the presence of an intracranial mass lesion, resuscitation with 3%-HSS prevented an increase in ICP while resuscitation with isotonic saline or colloid solutions markedly elevated ICP [4]. Qureshi *et al.* [15] demonstrated that a single dose of HSS effectively reduced the intraparenchymal pressure in all regions of the brain in dogs with experimental intracerebral hematoma. However, there is enough ground for controversy about the duration time of HSS effect such as lowering ICP. A 7.2% HSS was demonstrated to ICP for 98 ± 14 min in rabbits with experimental elevations in ICP [1] and for 2 hr at least in humans with traumatic brain injury [11]. It is important that duration of time that water movement by HSS administration becomes clear to make a treatment protocol to restore brain edema in dog. Mechanisms by which HSS reduces ICP could come from the establishment of an osmotic gradient between the intravascular space and the regions of non-injured tissue where the blood-brain barrier is intact. This osmotic gradient would drive water from the intra- and extra-cellular spaces in the brain into capillaries, hence lessening intracranial volume and ICP [11]. Especially, an increase in plasma sodium concentration by HSS infusion significantly decreases ICP and increases cerebral perfusion pressure [6]. It is important to measure the dynamics of sodium ion that determine osmotic pressure for evaluating dynamics of water and the duration of water movement during the initial period of resuscitation by HSS infusion. However, there have been few literatures concerning what effect HSS infusion has on the gradient of sodium concentrations between cerebrospinal fluid (CSF) and the venous blood.

The aims of this study were to determine the gradient of sodium concentrations between venous blood and CSF, which causes the water movement from the intracellular and cerebrospinal spaces into capillaries in brain, and to determine how long it maintains sodium gradients of the CSF become equivalent to the sodium gradient in the capillaries.

All procedures were in accordance with the National Research Council Guideline for the Care and Use of Laboratory Animals [12]. Experiments were performed on 3 male and 2 female 2.6 ± 0.9-year-old Beagles (mean ± SD), weighing 11.4 ± 1.8 kg (mean ± SD). These dogs were deemed healthy on the basis of a physical examination, thoracic auscultation, and radiological and echocardiographic analysis. The experiment was conducted using a 2 × 2 Latin Square design and resting interval between experiments was more than 1 month. Each dog was given two treatments as follows: the HSS group was given HSS (7.2%-NaCl, IV infusion of 5 m*l*/kg) and the ISS group was given isotonic saline solution (0.9%-NaCl, ISS, IV infusion of 5 m*l*/kg) at

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a flow rate of 20 m*l*/kg/hr. The order of treatment was at random. Approximately 15 min before anesthesia, 22-gauge, 2.5-cm long catheters (Terumo Co., Tokyo, Japan) were inserted into both cephalic veins. The catheter in the right cephalic venous was used for fluid infusion, and the other in the left venous was for collecting blood samples. Each dog was anesthetized by thiopental sodium (Ravonal 0.3 for injection, Tanabe Seiyaku, Osaka, Japan) at a dose of 15 mg/kg IV, and intubated orally, put under anesthesia with isoflurane and maintained on 100% oxygen throughout the experiment with 2.0 MAC isoflurane (Forane; Abbott Laboratory, Illinois, U.S.A.). Immediately after the dogs were anesthetized, a 22 gauge spinal needle (22 × 2–1/2; Becton-Dickinson, New Jersey, U.S.A.) was inserted into Cysterna magna for collection of CSF at each sampling point.

Venous and CSF samples were collected immediately before fluid infusion (pre), and after 15, 30, 45, 60, 90 and 120 min of fluid infusion. Venous and CSF samples were collected in heparinized and unheparinized 1 m*l* syringes, respectively, and the tips of syringes were capped. Immediately after the collection, venous and CSF samples were analyzed for sodium and chloride concentrations with an automatic analyzer (Bayel 348, Bayel Medical Co., Tokyo Japan). Some blood samples were used to determine hemoglobin concentration (Hb) and hematocrit value (Ht) by an automatic cell counter (Celltac Alfa, Nihon Kohden Co., Tokyo, Japan). Changes in the relative plasma volume (rPV) were calculated from Hb and Ht, using the accepted formula [3, 19, 20].

Data are presented as mean ± standard deviation (SD). Measured dependent variables, including rPV and electrolyte concentrations, were compared between the two groups for each sample collection period, using repeated-measures two-way ANOVA. Within groups, mean values for each dependent variable were compared with the pre values, using the Bonferroni test after analysis of repeated measured two-way ANOVA. A value at $p<0.05$ was considered significant.

Table 1 shows the sequential changes in the rPV, and venous and CSF electrolyte concentrations in the dogs infused HSS or ISS. The rPV in the ISS group increased significantly, reaching 110.1 ± 3.3% at t=15 min when the fluid infusion was completed, and this value recovered to the pre value at t=30 min. In contrast, significant increase in the rPV was observed in the HSS group, which reached a peak of 123.5 ± 3.9% at t=15 min. A significant increase in rPV was maintained for the rest of the experiment.

Neither the venous or CSF sodium concentrations were altered by ISS infusion at any time during the experiment. In contrast, HSS infusion induced a progressive and significant increase in venous sodium concentration was observed, reaching a peak of 163.0 ± 2.2 mM at t=15 min. This increase remained for the duration of the experiment. A significant increase in the CSF sodium concentration was observed at t=45, 60, 90 and 120 min, reaching peak of 156.8 ± 5.0 mM at t=90 min. The venous sodium concentration remained at a higher value than that in the CSF until t=90 min after HSS infusion when CSF sodium concentration became equal to that in venous blood. A significant increase in the venous-CSF sodium differences was observed at t=15 and 30 min, reaching peak of 13.0 ± 0.7 mM at t=15 min, compared with pre-value 0.8 ± 2.2 mM.

Although venous chloride concentration increased significantly at t=30 and 45 min by ISS infusion, this change returned to baseline values at t=120 min. In contrast, a progressive increase in venous chloride concentration was

Table 1. Relative plasma volume and electrolytes alternations of 7.2% Hypertonic Saline Solution (HSS) administered IV in dogs

		pre	15	30	45	60	90	120 (min)
Relative Plasma Volume (%)[a)]								
	ISS	100	110.1 ± 3.3*	107.1 ± 1.9	105.4 ± 5.4	104.5 ± 6.0	103.1 ± 6.0	100.2 ± 7.3
	HSS	100	123.5 ± 3.9*	117.2 ± 8.0*	113.5 ± 6.8*	112.8 ± 3.9*	110.7 ± 2.1*	111.0 ± 5.7*
Sodium concentration (mM)								
venous[a)]	ISS	148.0 ± 0.7	147.8 ± 0.4	148.0 ± 0.7	148.0 ± 0.7	147.8 ± 1.1	147.3 ± 1.3	147.5 ± 0.9
	HSS	148.6 ± 2.3	163.0 ± 2.2*	159.4 ± 2.4*	158.2 ± 2.6*	157.4 ± 2.6*	156.8 ± 3.0*	155.8 ± 2.3*
CSF[a)]	ISS	146.8 ± 0.8	147.0 ± 0.0	147.2 ± 0.4	147.2 ± 0.4	147.0 ± 0.0	147.2 ± 0.4	147.6 ± 0.5
	HSS	147.8 ± 2.4	150.0 ± 2.1	152.6 ± 1.5	153.8 ± 1.9*	155.2 ± 1.9*	156.8 ± 5.0*	156.6 ± 2.6*
Venous-CSF	ISS	1.2 ± 0.4	0.5 ± 0.5*	0.6 ± 0.5*	0.8 ± 0.4	0.8 ± 1.1	0.0 ± 0.2	0.2 ± 0.2
Differences[a)]	HSS	0.8 ± 2.2	13.0 ± 0.7*	5.2 ± 3.1*	3.8 ± 1.0	2.2 ± 1.1	0.0 ± 2.2	–0.8 ± 0.8
Chloride concentration (mM)								
venous[a)]	ISS	116.3 ± 1.5	119.8 ± 1.5	119.5 ± 3.4	120.0 ± 3.6	116.0 ± 2.9	112.6 ± 0.9	112.8 ± 1.8
	HSS	115.2 ± 2.8	133.6 ± 3.2*	127.4 ± 2.6*	128.0 ± 2.3*	129.8 ± 1.6*	126.6 ± 1.1*	128.0 ± 1.6*
CSF[a)]	ISS	132.5 ± 0.9	135.3 ± 3.3	138.3 ± 3.5*	138.8 ± 3.8*	134.2 ± 3.2	130.0 ± 3.2	128.8 ± 1.9
	HSS	134.4 ± 1.8	137.4 ± 3.2	140.0 ± 3.5	140.0 ± 5.5	142.8 ± 2.5*	143.0 ± 2.1*	141.8 ± 3.8*
Venous-CSF	ISS	–16.2 ± 0.8	–14.4 ± 3.1	–18.1 ± 2.7	–18.8 ± 1.3	–18.2 ± 1.5	–17.4 ± 3.5	–15.3 ± 2.4
Differences[a)]	HSS	–19.2 ± 2.6	–3.8 ± 4.1	–13.3 ± 3.1	–13.0 ± 5.5	–13.0 ± 2.7	–16.4 ± 2.6	–13.8 ± 3.0

CSF: cerebrospinal fluid. Levels of significance indicated. a): $p<0.05$, ISS vs. HSS by 2-way ANOVA, *: $p<0.05$, vs. pre value by Bonferroni test.

observed after HSS infusion. The venous-CSF chloride differences closed significantly by HSS infusion reaching peak of –3.8 ± 4.1 mM at 15 min, compared with pre-value –19.2 ± 2.6 mM. The venous-CSF chloride differences returned to pre-value at 90 min, concurrent with CSF sodium concentration became equal to that of venous blood. Venous and CSF potassium concentration were not changed significantly by ISS and HSS infusion. In this study, the duration of time that water moved from the CSF into intravascular space as a result of the sodium gradient was 90 min. This time is similar and supported the results by Berger *et al.* [1]. Therefore, it is suggested that HSS infusion alleviates brain edema for 90 min. This result may help to make a treatment protocol to restore a brain edema in dogs.

These conclusions are based on a relationship between serum sodium and ICP. Direct comparison with colloid solutions such as dextran and hydroxyethyl starch demonstrated that HSS is superior to colloids in regard to ICP response during the initial period of resuscitation [14]. The differences in response dose not seem to be related solely to the difference in osmolality, but other mechanisms may be involved. Khanna *et al.* [6] determined whether there is a statistical relationship between ICP and serum sodium used by polynomial regression models and then demonstrated that a relationship exists between serum sodium and ICP. One explanation may be that sodium ion pumps prevent intracellular accumulation of sodium and chloride during the initial period of resuscitation [5]. Additional studies that directly measure actual gaps of the pressure and osmolality between venous and CSF before definitive recommendations can be make regarding the optimal fluid to use for initial resuscitation of dog with brain edema.

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