

## Administration of Large Volume Hypertonic Solutions for Resuscitation of Hemorrhagic Shock in Rabbit

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### ABSTRACT

An animal model was designed to study the effect of large volume Hypertonic Solutions (HTS) for resuscitation following a hypovolemic shock. Resuscitation in hypovolemic animals was performed by infusion of 15 ml/kg of normal saline (group I), 5% sodium bicarbonate (NaHCO<sub>3</sub>); (group II), 5% sodium chloride (NaCl) and 7.5 % NaHCO<sub>3</sub>; 1:1 VN (group III), 5% NaCl (group IV), and 5% NaCl and 5% serum albumin; 2:1 VN (group V) via jugular vein. All animals were monitored sixty minutes post infusion. Then they were sacrificed to determine Brain Water Content (BWC), pathological investigation of heart, aorta and pulmonary tissues. Two other groups were also used for determination of normal BWC (group N) and aftershock BWC (group S). Mean Arterial Pressure (MAP) of groups H, IV and V were statistically different from group I ( $P < 0.05$ ). Albumin concentration and urine output were increased markedly in group V ( $P < 0.05$ ). Serum osmolality in groups III, IV, and V were significantly different from the first group ( $P < 0.05$ ). Acid-base parameters in groups II and III were raised toward normal, and they showed significant differences from group I ( $P < 0.05$ ). BWC were decreased in groups treated with HTS ( $p < 0.05$ ). No statistical differences were observed in pulse pressure, heart and respiration rates, sodium and potassium concentrations, and urine osmolality between the groups. No detectable pathological changes were observed in heart, aorta and pulmonary tissues. *Iran. Biomed. J. 2: 71-77, 1998*

**Keywords:** Hemorrhagic shock, Hypertonic solution, Blood pressure, Acidosis, Urinary output

### INTRODUCTION

Recently there have been increased interest of HTS with various concentration in initial resuscitation from hemorrhagic shock [1-6]. Hemorrhagic shock is associated with reduction of urine output and venous return. Lactic acidosis is a commonest disturbance of acid-base disorders in hypovolemic shock. Base Excess (BE) as an indicator of blood volume deficit, plays an important role in trauma patients [7]. It is correlated with lactate level during hemorrhagic shock and resuscitation [8]. It has been reported that HTS increase the systemic MAP, and renal and coronary blood flows [9, 10]. HTS produce high osmotic forces in intravascular compartment which let the fluid move out from intracellular space into intravascular compartment. Resuscitation with hypertonic NaCl cannot improved acidosis, but Velasco et al. compared hypertonic NaCl (2400 mosmole/l) with isotonic NaCl (300 mosmole/l) resuscitation in animal model with severe hemor-

rhagic shock, and they reported a better correction of pH and BE in hypertonic resuscitation [11]. It has also been reported that NaHCO<sub>3</sub> improves pH, bicarbonate ion (HCO<sub>3</sub><sup>-</sup>) concentration and Carbon Dioxide Partial Pressure (PCO<sub>2</sub>) in patients with lactic acidosis [12]. The elevation of plasma colloid osmotic pressure also plays an important role in increasing extracellular fluid compartments. Lucas et al. had compared the plasma volume and renal excretory function in two groups of albumin and non-albumin resuscitation, and elevation of plasma volume and reduction in urine output were reported in albumin treated patients [13]. The effect of 5% albumin on renal function indicates the lower Urine Output (UO) in comparison with ringer lactate resuscitation [14]. The effect of HTS on BWC and Intracranial Pressure (ICP) has been investigated with various experimental designs [15-18]. It had been demonstrated that HTS can reduce ICP. Resuscitation with HTS is still under investigation [5, 6]. This study is carried out to compare large volume

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of HTS with saline resuscitation following acute hemorrhage in an animal model.

## MATERIALS AND METHODS

Forty two of *Lepouse Americanus* rabbits of either sex (mean weight  $1.662 \pm 0.034$  kg) were divided in seven groups. After an overnight food fast, the induction was performed with 0.5-1.5 ml of 5% thiopental sodium (SPECIA, France) injected into ear vein and anesthetization was continued with mixture of ether (May & Baker LTD, England) and oxygen. The left and right femoral arteries were cannulated for continuous monitoring of blood pressure with a transducer (HSE-Druck-Koppler, type 551A, Hugo Sachs Elektronik, Germany) and for bleeding to obtain an acute hemorrhage. Left jugular vein was also cannulated for fluid infusion. Bladder was emptied completely, and a dose of 1000 IU/kg of heparin (LEO, Denmark) was injected via femoral artery for prevention of blood coagulation. Anesthetic agent was stopped, and the animals were left to breath from room air. Hemorrhagic shock was induced by rapid bleeding in 3-7 minutes to reduced the MAP to 40-45 mmHg. MAP was maintained in this level of hypotension for forty five minutes by addition or withdrawal of blood as needed (end of shock). At this time (45 minutes post hemorrhage), the first arterial blood sample was obtained. The sample was analyzed for blood gas parameter (pH; Oxygen Partial Pressures,  $PO_2$ ;  $PCO_2$ ;  $HCO_3$ ; BE; Buffer Base, BB; and Oxygen Saturation,  $SO_2$ ) by a blood gas analyzer (Model AVL). Serum sodium and potassium (KONE flame photometer), serum albumin and Total Protein (TP) concentration (Ependroff ELAN analyzer), serum and urine osmolalities (Model #15500 Wescor Osmometer) were also measured. UO also was collected from the bladder for osmolality measurement and volume calculation. Then the hemorrhagic animals were treated with 15 ml/kg of following solutions via jugular vein for period of 15 minutes (HTS were obtained from The Pasteur Institute of Iran).

Group I (n=6): normal saline.

Group II (n=6): 5%  $NaHCO_3$ .

Group III (n=6): 5% NaCl and 7.5 %  $NaHCO_3$  (1:1 VN).

Group IV (n=6): 5% NaCl.

Group V (n=6): 5% NaCl and 5% serum albumin (2:1 VN).

The animals were monitored sixty minutes post infusion. MAP, Pulse Pressure (PP), Respiration Rate (RR), and Heart Rate (HR) were determined every fifteen minutes. Final blood sample and UO were taken at the end of experiment for required measurements. Then all animals were sacrificed. Brains were rapidly removed for determination of BWC by wet/dry weight method [5]. The early effect of HTS on Heart, aorta and pulmonary tissues were also considered with pathological investigations. Two other groups of animals were used for normal and shock BWC determination. Normal BWC animals (group N, n=6) were anesthetized and sacrificed. The brains were rapidly removed for determination of normal BWC. Shock BWC animals (group S, n=6) were followed with the same procedures, already describe for groups I to V except with no treatment. The animals of this group were sacrificed for BWC determination 45 minutes post hemorrhage (end of shock). The groups S and N also were subjected to tissues pathological considerations.

**Statistical Analysis.** The results are reported as mean  $\pm$  SE. MAP, PP, RR, and HR were compared statistically in five groups after fluid infusion using analysis of variance for repeated measurements. Comparisons of other data between the groups were made with one way analysis of variance. If a significant F ratio was found, then a multiple comparison (Student-Newman-Keuls method) was performed to determine significant difference between the groups. Statistical values of less than 0.05 were considered as significant.

## RESULTS

In order to maintain the MAP at level of 40-45 mmHg, the withdrawn blood volume was  $18.41 \pm 0.49$ ,  $21.61 \pm 1.61$ ,  $18.43 \pm 1.51$ ,  $19.9 \pm 1.01$ , and  $20.95 \pm 1.19$  milliliter per kilogram of weight in groups I, II, III, N, and V respectively, and no significant difference was existing between the groups.

Figures 1 and 2 show MAP, and PP in the experimental groups. The results indicate a significant difference in MAP between the groups ( $P < 0.05$ ). MAP in groups II, IV and V was significantly different from group I ( $P < 0.05$ ). No statistical differences were detected in PP, RR, and HR between the groups. Albumin had raised markedly (Table 1) in group V, and it was different

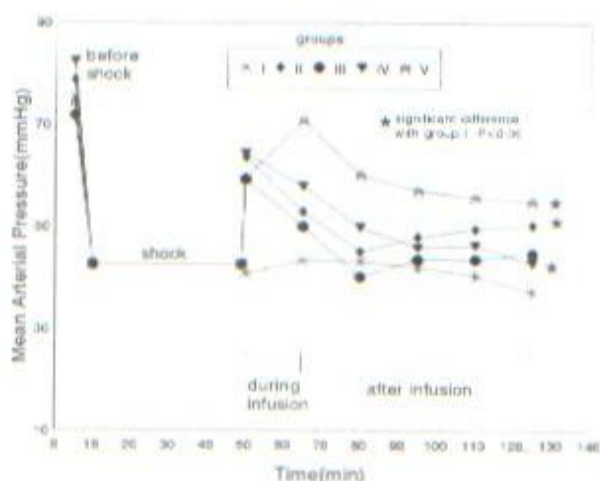


Fig. 1. Time related changes in MAP. A significant difference was existing in groups II, IV and V from group I ( $P < 0.05$ ).

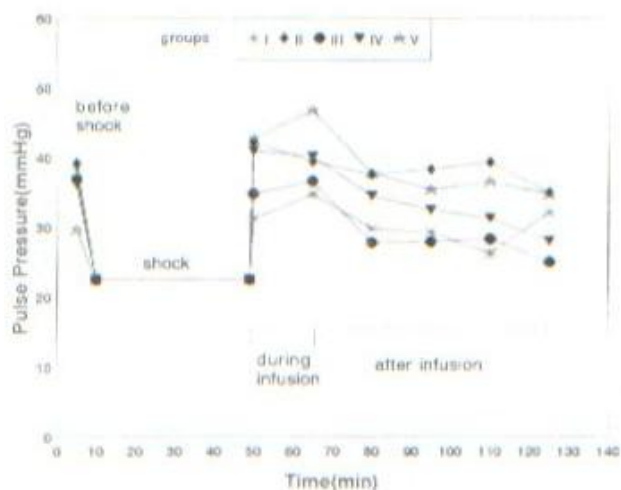


Fig. 2. Time related changes in PP. No significant difference was existing between the groups.

statistically with groups I, III and IV ( $P < 0.05$ ). Large UO was obtained in groups II, III, IV and V which were statistically different from first group ( $P < 0.05$ ).  $\text{HCO}_3^-$  concentration, BB and BE concentrations in groups II and III had increased toward normal, and they were different from groups I, IV and V significantly ( $P < 0.05$ ). pH in groups II and III had increased toward normal. This parameter in group II was different from groups I, IV and V ( $P < 0.05$ ), but the third group pH indicate a difference

from group IV only ( $p < 0.05$ ). A significant difference was obtained between first group  $\text{PCO}_2$  and second & third groups ( $p < 0.05$ ). After resuscitation, the serum osmolalities in experimental groups of III, IV and V were more than the first group ( $p < 0.05$ ). There were also a difference in  $\text{SO}_2$  between groups III and IV ( $P < 0.05$ ). For other parameters in Table 1, there were not significant differences.

The experimental data for all groups BWC is shown in figure 1. The results indicate that significant reduction of BWC in groups II, III, IV, and V were obtained ( $p < 0.05$ ). Hemorrhagic shock without treatment (group S) and resuscitation with normal saline (group I) did not change BWC significantly. Therefore BWC in groups I and S were not different from normal BWC (group N). No detectable pathological changes were observed in heart, aorta and pulmonary tissues between the groups.

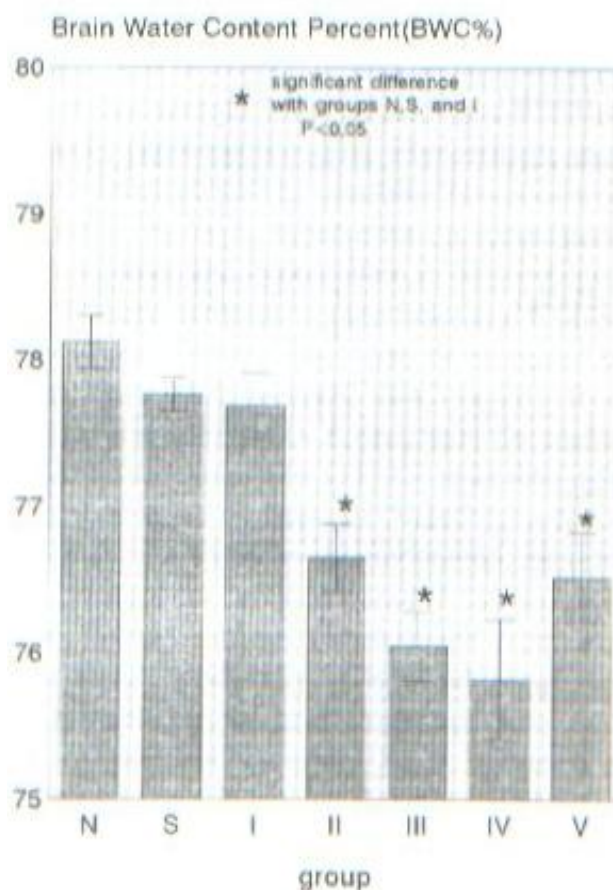


Fig. 3. BWC in normal, shock, and experimental treated groups. Significant reduction of BWC was obtained in groups II, III, IV and V ( $P < 0.05$ ).

**Table 1.** Blood gas parameters, sodium, potassium, albumin, and TP concentrations, serum and urine osmolality, and UO at forty five minutes post hemorrhage (end shock) and sixty minutes post infusion (end resuscitation) in the five groups of animals.

Parameter	Group	End shock		End resuscitation	
Sodium (meq/l)	I	150.16 ± 1.22		157.66 ± 4.12	
	II	152.30 ± 2.24		164.50 ± 1.44	
	III	146.80 ± 1.77	NS	168.00 ± 3.20	NS
	IV	150.83 ± 5.52		167.66 ± 2.99	
	V	153.00 ± 1.39		170.66 ± 2.68	
Potassium (meq/l)	I	3.63 ± 0.25		3.72 ± 0.26	
	II	3.37 ± 0.19		3.17 ± 0.43	
	III	3.57 ± 0.21	NS	3.66 ± 0.44	NS
	IV	3.72 ± 0.33		4.24 ± 0.52	
	V	4.30 ± 0.90		3.93 ± 0.64	
Albumin (g/dl)	I	3.11 ± 0.11		2.86 ± 0.11	
	II	3.22 ± 0.14		3.14 ± 0.19	
	III	3.05 ± 0.11	NS	2.72 ± 0.13	S
	IV	3.09 ± 0.13		2.63 ± 0.12	
	V	3.23 ± 0.13		3.55 ± 0.13	*\$@
TP (g/dl)	I	5.52 ± 0.26		4.79 ± 0.23	
	II	5.56 ± 0.20		5.32 ± 0.37	
	III	5.06 ± 0.27	NS	4.49 ± 0.26	NS
	IV	5.19 ± 0.26		4.52 ± 0.27	
	V	5.18 ± 0.20		5.19 ± 0.24	
pH	I	7.290 ± 0.03		7.298 ± 0.07	
	II	7.249 ± 0.03		7.482 ± 0.02	*@&
	III	7.257 ± 0.02	NS	7.375 ± 0.03	@S
	IV	7.219 ± 0.32		7.181 ± 0.67	
	V	7.281 ± 0.25		7.241 ± 0.46	
PCO <sub>2</sub> (mmHg)	I	24.40 ± 3.0		20.50 ± 1.90	4\$
	II	27.63 ± 2.39		31.03 ± 2.39	
	III	27.51 ± 1.69	NS	29.30 ± 2.61	S
	IV	24.46 ± 2.97		25.98 ± 2.27	
	V	24.34 ± 2.13		26.16 ± 1.61	
PO <sub>2</sub> (mmHg)	I	83.83 ± 3.45		100.3 ± 3.48	
	II	94.35 ± 3.78		94.2 ± 5.40	
	III	98.10 ± 5.01	NS	104.9 ± 5.61	NS
	IV	93.18 ± 3.80		99.4 ± 5.28	
	V	86.02 ± 8.26		93.1 ± 4.53	
SO <sub>2</sub> (%)	I	93.43 ± 1.35		96.68 ± 0.26	
	II	94.71 ± 0.83		97.63 ± 0.42	
	III	95.60 ± 0.40	NS	97.51 ± 0.37	@S
	IV	93.80 ± 1.23		92.18 ± 1.90	
	V	92.08 ± 3.37		93.63 ± 2.16	
BE (mmol/l)	I	-12.88 ± 1.04		-13.90 ± 1.34	
	II	-13.70 ± 1.30		0.88 ± 1.43	*\$@&
	III	-13.11 ± 1.70	NS	-6.23 ± 2.27	*@&S
	IV	-15.96 ± 1.62		-19.76 ± 1.82	
	V	-13.30 ± 1.35		-14.30 ± 2.01	
BB (mmol/l)	I	35.01 ± 1.05		34.00 ± 1.34	
	II	34.20 ± 1.30		48.83 ± 1.45	*\$@&
	III	34.78 ± 1.70	NS	41.68 ± 2.89	*@&S
	IV	31.93 ± 1.62		28.13 ± 1.82	
	V	34.60 ± 1.35		33.60 ± 2.01	

HCO <sub>3</sub> (mmol/l)	I	11.16 ± 1.08		9.80 ± 0.98	
	II	11.68 ± 0.96		22.43 ± 1.47	*\$@&
	III	12.16 ± 1.39	NS	16.98 ± 2.07	*@& S
	IV	9.76 ± 1.28		8.25 ± 0.79	
	V	11.10 ± 1.09		11.13 ± 1.13	
UO (ml)	I	1.58 ± 0.47		0.88 ± 0.26	#\$@&
	II	0.85 ± 0.27		16.91 ± 5.35	
	III	1.53 ± 0.54	NS	19.58 ± 3.91	
	IV	1.58 ± 0.43		16.46 ± 4.50	
	V	0.80 ± 0.46		32.58 ± 3.11	*#\$@
Osmolality (mosmol/kg) serum	I	309.58 ± 4.03		316.52 ± 5.63	
	II	306.20 ± 4.34		329.10 ± 5.40	
	III	301.50 ± 5.01	NS	340.20 ± 4.13	* S
	IV	316.00 ± 7.35		351.50 ± 6.47	*#
	V	309.00 ± 1.95		337.16 ± 3.06	*
Urine	I	868.2 ± 86.34		537.0 ± 38.37	
	II	1068.8 ± 151.3		427.3 ± 24.80	
	III	960.0 ± 83.6	NS	473.4 ± 28.6	NS
	IV	1018.0 ± 72.0		450.9 ± 20.0	
	V	1008.0 ± 81.0		473.5 ± 26.0	

(S), Significant difference;  $P < 0.05$ . NS, Non-significant difference;  $P > 0.05$ . \*, Statistical difference with group I. #, statistical difference with group II. (\$), Statistical difference with group III. (@), statistical difference with group IV. (&), statistical difference with group V.

## DISCUSSION

Restoration of intravascular fluid compartment is the main purpose of hypovolemic shock. After resuscitation, the MAP had significantly raised in groups II, IV and V, but no statistical differences were observed in PP, RR, and HR. Increasing of MAP immediately after resuscitation with HTS was reported [19]. Behrman et al. compared 4 ml/kg of 7.5% saline resuscitation with 16 ml/kg of lactated ringer in an animal experiment, and they also found significantly elevated of MAP immediately after infusion, but there were no differences existing by two hour [2]. Addition of albumin to HTS may decrease capillary filtration during resuscitation which results in a better maintenance of plasma volume. In two groups of critically ill patients who received pure NaHCO<sub>3</sub> and isotonic NaCl solutions, MAP was relatively unchanged [12]. The UO in HTS resuscitation groups was more than group I. It had been reported that HTS increase renal blood flow and urine secretion [9, 19]. Our results for UO in group V are different from findings of other investigators [13, 14]. It seems that elevation of UO in group V is caused by produced high MAP after

resuscitation. Serum osmolality was increased in groups III, IV and V, but sodium concentration did not change significantly. Non-significant differences for sodium, potassium, and TP also were found by others in treated hemorrhagic shock animal with 7.5% NaCl and NaHCO<sub>3</sub> [20]. It is clear that, serum sodium and osmolality levels are related to resuscitated fluid osmolality. Small elevation in sodium in last group may be related to its binding to albumin. Large volume of HTS resuscitation in this study did correct the induced acid-base disorder due to shock in groups II and III. Hemorrhagic shock is always accompanied by a metabolic acidosis which is induced by tissue hypoperfusion. Coexistence of lactic acidosis and hypotension in hemorrhagic victims disturbs the body organs functions. Correction of acid-base disorder may not be produced by resuscitation with hypertonic NaCl rapidly. It seems that infusion of NaHCO<sub>3</sub> is necessary for correction of acid-base parameters [11, 12] after hemorrhagic shock, but small volume of NaHCO<sub>3</sub> solution by itself may not improve hemodynamic disturbance [12]. Prough et al. compared 7.5% saline with ringer lactate during resuscitation from hemorrhagic shock, and they did not find any difference in PO<sub>2</sub>

level [21]. BE is an important factor in diagnosis of metabolic acidosis [8,22]. Elevation of albumin in group V caused elevation of plasma BB.  $\text{NaHCO}_3$  resuscitation in group II raised pH,  $\text{HCO}_3^-$ , BE, and BB from a metabolic acidosis. These results confirm findings of other investigators [12, 20, 23]. Resuscitation with pure hypertonic NaCl may lower pH slightly, but it induces a better perfusion and it may increase arterial  $\text{PO}_2$  [24]. Graf et. al. reported a higher gut lactate production with  $\text{NaHCO}_3$  in comparison with NaCl therapy [25]. Our blood gas analysis indicates that  $\text{NaHCO}_3$  resuscitation induces slight metabolic alkalosis, and its combination with high osmolality NaCl promotes the acid-base disorder toward normality. BWC reduction was one of the disadvantages of large volume HTS resuscitation. Animals in saline resuscitation (group I) and shock without treatment (group S) did not indicate any BWC reduction. Our findings support the idea that reduction of MAP to 40-45 mmHg for 45 minutes may not change BWC significantly, and infusion with high fluid osmolality reduce BWC as long as capillary membrane is not damaged. Microscopic pathological studies of the tissues did not indicate any change, but for detail investigation, the electron microscopic study is suggested to detect the early effect of HTS resuscitation. Finally, advantages and disadvantages of large volume HTS resuscitation after hemorrhagic shock must be evaluated precisely. Of course more study is needed for detail investigations, and side effects of resuscitation with large volume of HTS.

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