

CONTINUOUS INFUSION OF SMALL-VOLUME FLUID RESUSCITATION IN THE TREATMENT OF COMBINED UNCONTROLLED HEMORRHAGIC SHOCK AND HEAD INJURY

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ABSTRACT

Objective: To determine the effect of continuous limited fluid resuscitation on the hemodynamic response and survival in rats in a model of uncontrolled hemorrhage shock due to Massive Splenic Injury (MSI) and Head Injury (HI).

Design: An experimental study.

Place and Duration of Study: Dicle University Animal Research Laboratory, Turkey, between January and February 2005.

Subjects and Methods: Seventy Sprague-Dawley rats were used in this study. Group 1 rats (n=10) was sham-operated. In group 2 (n=10), only Massive Splenic Injury (MSI) was performed and untreated. In group 3 (n=10), only head injury (HI) was performed and untreated. In group 4 (n=10), HI and MSI were performed and were untreated. In group 5 (n=10), HI and MSI were performed and 15 minutes later treated with 7.5% NaCl. In group 6 (n=10), HI and MSI were performed, and rats were treated with Ringer's Lactate (RL) solution. In group 7 (n=10), HI and MSI were performed, rats were treated with 0.9 % NaCl. In groups 2,4,5,6 and 7 midline incision was reopened and splenectomy was performed at 45 minutes.

Results: In group 4 rats, Mean Arterial Pressure (MAP) was decreased from 104 ± 6.1 mmHg to 75 ± 19.5 mmHg at 15 minutes; heart rate decreased from 357 ± 24.9 beats/min to 321 ± 62.1 beats/min and hematocrit decreased from 46 ± 1.3 % to 43 ± 2.5 % ($p < 0.01$). Similar early changes in MAP, heart rate and hematocrit were observed in groups 5, 6, and 7, at 15 minutes. At 45, 60 and 120 minutes, in fluid resuscitated rats (group 5,6,7) MAP, heart rate and hematocrit values were measured higher than group 2 and 4 ($p < 0.01$ for all). At 120 min. in group 6, hematocrit was higher than group 4, 5 and 7, in group 6, total blood loss after splenectomy was calculated at 20 ± 2.4 % of blood volume and was the best value compared to other fluid resuscitated group 5 and 7 (28% and 27% of blood volume) ($p < 0.01$). Mortality was lower in all fluid resuscitated groups when compared to group 3 and 4 ($p < 0.05$). The median survival time was again higher in fluid resuscitated groups.

Conclusion: Continuous infusion of 7.5% NaCl, RL and 0.9 % NaCl following uncontrolled hemorrhagic shock with massive splenic injury and combined head injury resulted in better survival and RL did not increase abdominal bleeding before splenectomy was performed.

KEY WORDS: *Uncontrolled hemorrhagic shock. Head injury. Rat. Fluid resuscitation.*

INTRODUCTION

Fluids resuscitation to restore effective circulating volume following injury is a fundamental component of modern trauma care. The choice of fluid, the timing of fluid administration and the end points of fluid resuscitation in trauma patients remain controversial. Permissive hypotension may be appropriate in a case of penetrating trauma, but would adversely affect outcome in a severe closed head injury. Timing of fluid therapy in relation to definitive care is important.¹

Head injury is the main cause of trauma-related deaths in more than 60% of cases. Hemorrhage and shock are observed in upto 20% of the cases of patients with head injuries. Hypotension is a well-established cause of secondary

brain injury and contributes to a worsening outcome. Early and effective resuscitation is, therefore, essential for improved results. Under-resuscitation of patients with shock and an associated severe closed head injury decreases cerebral perfusion pressure, which causes secondary brain injury.²

Fluid resuscitation is often the first and only treatment for hypotensive patients. However, the mortality benefit of aggressive early fluid resuscitation has been questioned in the presence of uncontrolled hemorrhage in both animal models and human trials. However, many victims of trauma suffer multiple injuries including traumatic brain injuries.³⁻⁵ Traumatic brain injury can be worsened by even a single episode of hypotension.⁶ However, aggressive fluid resuscitation in uncontrolled hemorrhage is also harmful, resulting in increased hemorrhage volume and subsequently greater mortality.

There is continuing debate about the best fluid administration strategy in bleeding trauma patients. Multiple studies have investigated the effect of resuscitation by using hypertonic saline, normal saline and Ringers lactate in models of combined hemorrhagic shock and traumatic brain injury.^{2, 7-13} Studies using a standardized rat model of uncontrolled

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hemorrhagic shock induced by massive or moderate splenic injury in male rats demonstrated that bolus infusion of crystalloid or colloid solutions increased intra-abdominal bleeding and mortality.¹⁴⁻¹⁷ Hyperosmolar therapy has been used to reduce elevated intracranial pressure due to TBI. So the use of Hypertonic Saline (HTS) for resuscitation of head-injured patients has been approved.^{2,18}

This study was undertaken to determine the effect of HTS, small volume NS and small volume RL on mortality and amount of bleeding in a model of uncontrolled hemorrhage with massive splenic injury combined with closed head injury.

SUBJECTS AND METHODS

This experimental study was done in the Dicle University Animal Research Laboratory, Turkey, between January and February 2005. Seventy Sprague-Dawley rats, weighing between 300 and 359 grams, were used. All rats were housed in groups of three in standard cages, and kept with food and water ad libitum in a temperature-controlled room (22 °C) on a 12-hour dark/light cycle until surgical preparation. The research was approved by the Institutional Animal Care and Use Committee of the Technician Faculty of Medicine.

Rats were anesthetized with an intramuscular injection of 100 mg/kg ketamine HCl (Ketalar® Eczacıbaşı Istanbul). The animals were kept supine during the experiments, and body temperature was monitored with a rectal thermistor and maintained by external heating. In all rats, the carotid artery and the femoral vein were cannulated with polyethylene catheters (24F polimend, Polimedice Ltd, Brussels, Belgium) for blood pressure and pulse measurements, blood sampling, and intravenous fluid infusion. The arterial line connected to a calibrated pressure transducer and Data Acquisition System (Biopac Systems Model Mp 30). Heart rate was computed from the arterial tracing. Blood hematocrit was measured by a hematocrit centrifuge (Nüve sanayi Ltd. Ankara, Turkey). Fluid therapy was done with Ivack 770 infusion pump.

After anesthesia and cannulation, Marmarou *et al.*¹⁹ model was used for moderate diffuse head injury. A simple head injury device was designed to induce blunt trauma to the protected skulls of the rats. Midline scalp incision was performed, followed by periosteal elevation to expose the central area of the skull vault between the coronal and lambdoid sutures. A stainless steel disc, 1 cm in diameter, was firmly fixed by dental acrylic to this central portion of the skull vault. A cylindrical column of brass weighing 450g was allowed to fall through a 1-m Plexiglas tube onto a small rounded stainless steel disc fixed to the central portion of the skull vault of the rat. When the trauma device was ready, the rat was placed in prone position on a foam bed with the disc centered immediately under the lower end of the Plexiglas tube. The weight was allowed to drop freely from the 1 m height through the tube onto the disc. The cranial vault was inspected for the presence of any fracture. The scalp was sutured. Two rats died on impact and 2 with skull fractures were excluded from the study.

For hemorrhagic uncontrolled shock model a midline incision was performed and the splenic parenchyma was sharply transected transversely at two locations between the entrances of the major branches of the splenic artery into the spleen. Injury to splenic artery branches was avoided carefully, the cut edges of the spleen were allowed to bleed freely into

the peritoneal cavity, and the midline incision was closed. Fluid resuscitation was started after 15 minutes and splenectomy was performed after 45 minutes. Free intraperitoneal blood collected on preweighed piece of cotton immediately after splenectomy. The amount of blood loss was determined by the difference in wet and dry weights. Total blood loss was calculated as percent of total blood volume.

The animals were randomly divided into seven groups. Group - 1 (n = 10) was sham-operated. In group 2 (n = 10), only Massive Splenic Injury (MSI) was performed and was untreated and at 45 minutes splenectomy was performed and amount of free intraperitoneal blood was collected with a preweighed pieces of cotton. In group 3 (n =10) only head injury (HI) was performed and was untreated. In group 4 (n = 10) HI and MSI were performed and was untreated and at 45 minutes midline incision was reopened and splenectomy was performed. In group 5 (n = 10) HI and MSI were performed and 15 minutes later treated with 7.5 ml/kg/h of 7.5% NaCl (HTS), at 45 minutes midline incision was reopened and splenectomy was performed. The amount of free intraperitoneal blood was collected with a preweighed piece of cotton and abdomen was reclosed. In group 6 (n = 10) HI and MSI performed, rats were treated with 35 ml/kg/h of Ringer's lactate solution and again at 45 minutes splenectomy and collection of free blood were performed. In group 7 (n = 10) HI and MSI were performed, rats were treated with 35 ml/kg/h of 0.9 % NaCl and again at 45 minutes splenectomy and collection of free blood were performed.

The amount of volume to be infused for small volume infusion was determined from previous studies.^{20,21}

After 45 minutes from injury, splenectomy was performed in rats with massive splenic injury that were alive at that time. The animals were observed for 2 hours.

The mean arterial pressure (MAP), heart rate, hematocrit were determined just before head injury and/or laparotomy (time = 0) and at 15, 20, 30, 60, and 120, minutes after HI and/or MSI. Mean survival time in 2 hours was calculated.

All rats were sacrificed with cervical dislocation at the end of experiment.

Biostatistical evaluation was made using analysis of Variance (one-way ANOVA) with Tukey HSD honestly significant test for post hoc multiple comparisons using SPSS 10.0 software. The cumulative survival rate was analyzed by the Kaplan-Meier assay. Data were presented as the mean \pm SEM. A P value of < 0.05 was considered to be statistically significant.

RESULTS

Table I shows baseline values before and after head injury and /or massive splenic injury and treatment groups. Massive splenic injury in group 2 decreased the MAP, heart rate and hematocrit in 15 minutes ($p < 0.01$ for all). In group 3, MAP was increased at 15 minutes ($p < 0.05$); heart rate decreased ($p < 0.05$). In group 4 rats, MAP, heart rate and hematocrit was decreased at 15 minutes ($p < 0.01$). A similar early change in MAP, heart rate and hematocrit were observed in groups 5, 6, and 7 at 15 minutes. After 45, 60 and 120 minutes, in fluid resuscitated rats (group 5, 6, 7) MAP, heart rate and hematocrit values were measured higher than group 2 and 4

Table I. MAP, heart rate and hematocrit values in all rats.

	Time (min)	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7
MAP (mmHg)	00.00	117 ± 6.9	114 ± 7.3	114 ± 5.8	104 ± 6.1	107 ± 13.3	109 ± 7.7	123 ± 3.8
	15.00	117 ± 8.9	77 ± 9.3	118 ± 14.4	75 ± 19.5	84 ± 13.5	81 ± 34.7	105 ± 11.0
	45.00	114 ± 7.1	43 ± 16.4	87 ± 32.8	55 ± 4.0	72 ± 38.7	56 ± 4.1	66 ± 14.3
	60.00	112 ± 8.3	36 ± 18.4	105 ± 10.4	45 ± 11.2	101 ± 15.8	65 ± 6.6	87 ± 11.5
	120.00	112 ± 4.8	32 ± 10.3	87 ± 10.6	42 ± 8.4	109 ± 9.0	82 ± 8.3	108 ± 12.1
Heart rate (beats/min)	00.00	318 ± 11.3	345 ± 20.5	337 ± 17.5	357 ± 34.9	353 ± 17.5	360 ± 6.8	365 ± 15.3
	15.00	322 ± 8.8	312 ± 18.5	258 ± 83.1	321 ± 62.1	269 ± 19.4	266 ± 99.4	309 ± 82.9
	45.00	329 ± 8.8	198 ± 80.7	186 ± 75.7	215 ± 13.2	254 ± 94.7	205 ± 12.8	222 ± 69.1
	60.00	326 ± 16.8	185 ± 10.2	190 ± 14.1	206 ± 15.2	320 ± 23.0	267 ± 25.6	313 ± 19.2
	120.00	330 ± 6.3	204 ± 92.5	195 ± 13.2	188 ± 31.1	352 ± 16.1	319 ± 19.5	344 ± 18.3
HCT (%)	00.00	46 ± 1.0	46 ± 1.3	45 ± 1.0	46 ± 1.3	47 ± 1.0	47 ± 0.8	47 ± 1.3
	15.00	46 ± 1.3	42 ± 5.1	44 ± 1.2	43 ± 2.5	43 ± 1.2	43 ± 2.1	45 ± 2.0
	45.00	46 ± 1.3	30 ± 6.6	43 ± 1.5	36 ± 4.0	38 ± 1.8	38 ± 0.5	37 ± 2.0
	60.00	45 ± 0.8	29 ± 7.7	44 ± 2.8	30 ± 9.5	36 ± 0.5	37 ± 1.5	37 ± 2.8
	120.00	45 ± 0.4	28 ± 6.6	43 ± 1.4	33 ± 2.1	31 ± 5.8	37 ± 1.0	36 ± 3.7

($p < 0.01$). After 45 minutes, in group 4 heart rate was higher, MAP and hematocrit were lower than group 3 ($p < 0.05$). In group 5, MAP and heart rate were higher than group 6 and 7 but hematocrit was same. After 60 minutes, in group 4, heart rate was higher, MAP and hematocrit were lower than group 3 ($p < 0.05$). In group 5, MAP and heart rate were higher than group 6 and 7 but hematocrit was measured less. In group 6 and 7 rats, hematocrit values were measured higher than group 5, although, the values were very close to each other. After 120 minutes, in group 6, hematocrit was higher than group 4, 5 and 7 and MAP and heart rate were lower than group 5 and 7 but higher than group 4.

Total blood loss after splenectomy was calculated in RL group 20 ± 2.4 % of blood volume and was the best value compared to other fluid resuscitated group 5 and 7 (28% and 27 % of blood volume, $p < 0.01$). (Table I) No difference in blood loss was found between group 4 and 6. Mortality rates are showed in Table II. Mortality was lower in all fluid resuscitated groups when compared to group 3 and 4 ($p < 0.05$).

DISCUSSION

Appropriate fluid resuscitation in head injury with uncontrolled

Table II. Mortality rates and median survival time.

Groups	30 min (%)	60 min (%)	120 min (%)	Median survival time min
Control	0	0	0	120 ± 0.0
MSI	0	50	50	86 ± 16.3
Head injury	50	66.6	66.6	59 ± 20.3
HI+MSI	33.4	50	83.4	60 ± 17.4
HI+MSI+7.5% NaCl	33.4	50	50	77 ± 20.3
HI+MSI+RL- 35	33.4	50	50	84 ± 16.9
HI+MSI +0.9% NaCl 35	33.4	50	50	79 ± 20.0

hemorrhagic shock is still controversial. In uncontrolled hemorrhage, optimum survival is thought to be achieved by allowing blood pressure to remain low until surgical homeostasis is achieved, a technique known as 'permissive hypovolemia' or hypotensive resuscitation for which systolic BP of 70 - 80 mmHg has been suggested. This is not appropriate for head injury patients. Arterial hypotension and arterial hypoxia frequently accompanied by hypercapnia, result in subsequent secondary cerebral damage in most traumatic brain injury patients due to reduced tissue

oxygenation. That is why respiratory and circulatory resuscitation and stabilization must be the top-priority objectives of medical care of the traumatic brain injury patient.

In animal models, a number of authors suggested that aggressive fluid resuscitation, prior to hemostasis, increased bleeding because of increased arterial and venous pressure, dilution of clotting factors, and decrease in blood viscosity.^{14-17,22} Aggressive pre-operative fluid infusion is still considered appropriate for unconscious patients without palpable blood pressure or for those with controllable hemorrhage. However, some studies recommended limited or delayed intravenous fluid resuscitation pre-operatively in those with uncontrollable hemorrhage.^{23, 24} Currently, there is no clear cut universal consensus pertaining to the optimal resuscitation strategy in trauma patients. However, most prudent trauma surgeons propose that a policy of judicious fluid administration to maintain the MAP in the 60-80 mmHg range is advisable and appropriate. Fluid resuscitation in trauma should be considered a double edged sword and not the definitive therapy. In a number of trauma patients it is only a temporizing measure, until surgical control of bleeding can be achieved.²⁰ Talmor and colleagues investigated whether interventions to increase mean arterial pressure would improve neurologic outcome in a rat model of closed head trauma and/or uncontrolled hemorrhage.²⁵ Support of mean arterial pressure to 70, 80, or 90 mmHg with large volumes of saline worsened the neurologic defect score and/or survival. The present experimental design simulated a multiple-trauma clinical scenario with pre-hospital and early hospital phases. In this study, limited fluid infusion decreased mortality in all groups. Lactated Ringer's solution is a widely available, frequently used balanced salt solution, safe and inexpensive, which equilibrates rapidly throughout the extracellular compartment, restoring the extracellular fluid deficit associated with blood loss.²⁶ Ringer Lactate at 35 ml/kg/h dose decreased total abdominal blood loss when compared to other fluid resuscitated groups ($p < 0.01$). Both HTS and 0.9% NaCl infusion increased total abdominal bleeding when compared to non fluid resuscitated group 4 ($p < 0.01$).

There is continuing interest in the role of hypertonic saline during resuscitation from hypovolemic shock. A recent study pointed that the group treated with hypertonic solution in the early hospital phase evolved with better control of the ICP

when compared with the group treated with lactated Ringer's solution.² Bolus HTS infusion has been recommended for the initial fluid resuscitation of the hemorrhaging battlefield casualties by the Committee on Fluid Resuscitation for Combat Casualties formed by the Institute of Medicine of the National Academy of Science.²⁷ In this study HTS did not have any superiority to RL and normal saline for mortality rate. HTS even increased bleeding when compared to RL.

Patients sustaining closed head injuries rarely sustain hemorrhagic injuries that are very easy to control. It is suggested that for those patients with closed head injury and uncontrolled bleeding, continuous limited resuscitation with HTS, RL and NaCl would improve survival and RL infusion may be better than others due to less total bleeding.

CONCLUSIONS

The present results suggest that continuous limited resuscitation with RL after uncontrolled hemorrhage and severe head injury improve survival rate and amount of intra-abdominal bleeding. Hypertonic saline solution was not superior to RL or normal saline in improving survival.

Although abdominal bleeding were increased in HTS and NaCl infused rats, mortality rate was found lower in these groups compared to group 4. However, limited continuous resuscitation with RL decreased both the mortality rate and total abdominal bleeding.

REFERENCES

- Levett D, Vercueil A, Grocott M. Resuscitation fluids in trauma 1: why give fluid and how to give it. *Trauma* 2006; **8**: 47-53.
- Pinto FC, Capone-Neto A, Prist R, E Silva MR, Poli-de-Figueiredo LF. Volume replacement with lactated Ringer's or 3% hypertonic saline solution during combined experimental hemorrhagic shock and traumatic brain injury. *J Trauma* 2006; **60**: 758-64.
- Watters JM, Tieu BH, Differding JA, Muller PJ, Schreiber MA. A single bolus of 3% hypertonic saline with 6% dextran provides optimal initial resuscitation after uncontrolled hemorrhagic shock. *J Trauma* 2006; **61**: 75-81.
- Bickell WH, Bruttig SP, Millnamow G, O' Benar J, Wade CE. The detrimental effects of intravenous crystalloid after aortotomy in swine. *Surgery* 1991; **110**: 529-36.
- Bickell WH, Wall MJ, Pepe PE, Martin RR, Ginger VF, Allen MK, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med* 1994; **331**: 1105-9.
- Schreiber MA, Aoki N, Scott BG, Beck JR. Determinants of mortality in patients with severe blunt head injury. *Arch Surg* 2002; **137**: 285-90.
- Gibson JB, Maxwell RA, Schweitzer JB, Fabian TC, Proctor KG. Resuscitation from severe hemorrhagic shock after traumatic brain injury using saline, shed blood, or a blood substitute. *Shock* 2002; **17**: 234-44.
- Stern SA, Zink BJ, Mertz M, Wang X, Dronen SC. Effect of initially limited resuscitation in a combined model of fluid-percussion brain injury and severe uncontrolled hemorrhagic shock. *J Neurosurg* 2000; **93**: 305-14.
- Anderson JT, Wisner DH, Sullivan PE, Mattencio M, Freshman S, Hildreth J, et al. Initial small-volume hypertonic resuscitation of shock and brain injury: short-and long-term effects. *J Trauma* 1997; **42**: 592-601.
- Battistella FD, Wisner DH. Combined hemorrhagic shock and head injury: effects of hypertonic saline (7.5%) resuscitation. *J Trauma* 1991; **31**: 182-8.
- DeWitt DS, Prough DS, Deal DD, Vines SM, Hoen H. Hypertonic saline does not improve cerebral oxygen delivery after head injury and mild hemorrhage in cats. *Crit Care Med* 1996; **24**: 109-17.
- Sheikh AA, Matsuoka T, Wisner DH. Cerebral effects of resuscitation with hypertonic saline and a new low-sodium hypertonic fluid in hemorrhagic shock and head injury. *Crit Care Med* 1996; **24**: 1226-32.
- Walsh JC, Zhuang J, Shackford SR. A comparison of hypertonic to isotonic fluid in the resuscitation of brain injury and hemorrhagic shock. *J Surg Res* 1991; **50**: 284-92.
- Krausz MM, Semenikhina L, Hirsh M. Lactated Ringer's solution and hypertonic saline improve survival in uncontrolled hemorrhagic shock in female rats in metestrus. *J Surg Res* 2006; **132**: 23-31.
- Solomonov E, Hirsh M, Yahiya A, Krausz MM. The effect of vigorous fluid resuscitation in uncontrolled hemorrhagic shock following massive splenic injury. *Crit Care Med* 2000; **28**: 749-54.
- Krausz MM, Bashenko Y, Hirsh M. Crystalloid or colloid resuscitation of uncontrolled hemorrhagic shock following moderate splenic injury. *Shock* 2000; **13**: 230-5.
- Krausz MM, Bashenko Y, Hirsh M. Crystalloid and colloid resuscitation of uncontrolled hemorrhagic shock following massive splenic injury. *Shock* 2001; **16**: 383-8.
- Doyle JA, Davis DP, Hoyt DB. The use of hypertonic saline in the treatment of traumatic brain injury. *J Trauma* 2001; **50**: 367-83.
- Marmarou A, Foda MA, van den Brink W, Campbell J, Kita H, Demetriadou K. A new model of diffuse brain injury in rats. Part I: Pathophysiology and biomechanics. *J Neurosurg* 1994; **80**: 291-300.
- Hatoum OA, Bashenko Y, Hirsh M, Krausz MM. Continuous fluid resuscitation and splenectomy for treatment of uncontrolled hemorrhagic shock after massive splenic injury. *J Trauma* 2002; **52**: 253-8.
- Hatoum OA, Bashenko Y, Hirsh M, Krausz MM. Continuous fluid resuscitation for treatment of uncontrolled hemorrhagic shock following massive splenic injury in rats. *Shock* 2002; **18**: 574-9.
- Hai SA. Permissive hypotensive resuscitation: an evolving concept in trauma. *J Pak Med Assoc* 2004; **54**: 434-6.
- Stern SA, Zink BJ, Mertz M, Wang X, Dronen SC. Effect of initially limited resuscitation in a combined model of fluid-percussion brain injury and severe uncontrolled hemorrhagic shock. *J Neurosurg* 2000; **93**: 305-14.
- Bourguignon PR, Shackford SR, Shiffer C, Nichols P, Nees AV. Delayed fluid resuscitation of head injury and uncontrolled hemorrhagic shock. *Arch Surg* 1998; **133**: 390-8.
- Talmor D, Merkind V, Artru AA, Shapiro O, Geva D, Roytblat L, et al. Treatments to support blood pressure increases bleeding and/ or decreases survival in a rat model of closed head trauma combined with uncontrolled hemorrhage. *Anesth Analg* 1999; **89**: 950-6.
- Krausz MM. Initial resuscitation of hemorrhagic shock. *World J Emerg Surg* 2006; **1**: 14.
- Longnecker DE, Baxt WG, Fratantoni JC. Fluid resuscitation: state of the science for treating combat casualties and civilian injuries. Washington, DC: Inst Medicine 1999.