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Fluid therapy in uncontrolled hemorrhage

What experimental models have taught us

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ABSTRACT

Intravenous fluid is life-saving in hypovolemic shock, but fluid sometimes aggravates the bleeding. During the past 25 years, animal models have helped our understanding of the mechanisms involved in this unexpected effect. A key issue is that vasoconstriction is insufficient to arrest the bleeding when damage is made to a major blood vessel. “Uncontrolled hemorrhage” is rather stopped by a blood clot formed at the outside surface of the vessel, and the immature clot is sensitive to mechanical and chemical interactions. The mortality increases if rebleeding occurs.

In the aortic tear model in swine, hemorrhage volume and the mortality increase from effective restoration of the arterial pressure. The mortality *versus* amount of fluid curve is U-shaped with higher mortality at either end. Without any fluid at all, irreversible shock causes death provided the hemorrhage is sufficiently large. Crystalloid fluid administered in a 3:1 proportion to the amount of lost blood initiates serious rebleeding. Hypertonic saline 7.5% in 6% dextran 70 (HSD) also provokes rebleeding resulting in higher mortality in the recommended dosage of 4 ml/kg. Uncontrolled hemorrhage models in rats, except for the “cut tail” model, confirm the results from swine.

To avoid rebleeding, fluid programs should not aim to fully restore the arterial pressure, blood flow rates, or blood volume. For a hemorrhage of 1,000 ml, computer simulations show that deliberate hypovolemia (-300 ml) would be achieved by infusing 600-750 ml crystalloid fluid over 20-30 min or 100 ml of HSD over 10-20 min in an adult male.

Key words: hemorrhage, intravenous fluid, trauma, animal model, resuscitation, hypertonic saline dextran, hemostasis, mortality

Our body has a complex physiologic response to bleeding that initially involves vasoconstriction and a reduction in blood flow rates. Later, there is arterial hypotension, hypoperfusion, and acidosis. The infusion of fluids can reverse all these signs of a reduced circulating blood volume, a truly life-saving remedy. Fluid therapy is undoubtedly a most crucial component in the treatment of hemorrhagic shock.

However, in some instances, clinical experience holds that fluid therapy can make things worse. With the infusion of fluid, the hemorrhage accelerates and the patient is soon in a desperate situation where nothing helps. Clinical situations associated with such detrimental effects of plasma volume expansion include gastric bleeding and aortic rupture. Others might include traumatic pelvic fractures, gunshot wounds, and traffic accidents. Warnings about the hazards of ambitious fluid therapy in treating penetrating injuries were given as early as during World War I, but the pathophysiology of such untoward reactions to fluid therapy has still remained obscure.

Only the use of experimental animal models has been able to provide a better understanding of why infusion fluids sometimes have effects opposite to the intended ones. The present review summarizes how experimental studies have gradually increased our knowledge in this field. Together with fluid volume kinetic data derived from volunteers, they form a rational basis to current concepts of fluid therapy management in hypotensive patients suffering from hypovolemic shock where definite surgical treatment is not immediately available.

STUDIES IN PIGS

Most research models of hemorrhagic shock are based on a controlled biological system where a certain amount of blood is removed or exsanguination is performed down to a predetermined arterial pressure. Bickell, Bruttig, & Wade in 1989 developed an alternative hemorrhage model in swine, in which the bleeding is not controlled.¹ This model appeared to be more clinically relevant than the controlled models. The pig is widely used for studies of hemorrhagic hypotension and shock as the hemodynamic responses are very similar to man. Their blood hemoglobin is slightly lower (average

110 g/L)² and the coagulation system more effective than in humans.³

Anesthetized animals were surgically prepared and a needle, bent in a semicircle, was inserted into the aortic wall just below the kidneys. By pulling a wire affixed to the needle, the investigators could study the physiological consequences of an uncontrolled hemorrhage from a hole in the aorta having a width of exactly 0.5 mm.

When hemorrhage occurred in such a major central blood vessel, the animals responded in a way typical of later stages of hemorrhage, even before the amount of blood lost had reached appreciable amounts. There was no vasoconstriction and the systemic arterial pressure dropped within 10 seconds after the wire was pulled.¹ Other hemodynamic effects included a sharp drop in cardiac output (to 1/3 of baseline).

Riddez, Johnson, & Hahn improved the aortic tear model in 1998.^{2,4,5} By placing a flow probe above and below the site of the aortic tear, researchers could monitor the rate of the hemorrhage as the difference in flow between the two probes (Fig. 1). The experiments were further refined by providing immediate feedback to the investigators about the rate of the hemorrhage, allowing crystalloid fluid replacement that was more precise in terms of the amount of blood lost. These modifications addressed a drawback of previous work with volume-by-volume replacement when the investigators never knew exactly how much blood had been lost in an individual animal until autopsy had been performed.

The double flow probe method showed that the rate of the initial hemorrhage decreased in an exponential manner and stopped completely within 4 minutes (half-time 40 seconds) in a pig weighing 20 kg⁴ (Fig. 2). The total amount of blood lost during this early phase averaged 35% of the expected blood volume. However, after a variable time lapse, rebleeding often occurred; the number and intensity of these events determined the total blood loss and soon appeared to be a key factor promoting mortality.

Effect of arterial pressure

Susan Stern's research team used the aortic tear model to study the effect of the arterial pressure on mortality.⁶ Swine were bled from one femoral artery to a mean arterial pressure (MAP) of 30 mmHg after which the surgical steel aortotomy was induced. Fluid resuscitation with crystalloid fluid at a rate of 6 ml/kg/min maintained a MAP of 40 mmHg or 80 mmHg. The mortality was 13% and 63%, respectively, in these two groups, while 88% of the animals died when no fluid was infused. A 5-fold larger

intraperitoneal hemorrhage accompanied the higher mortality for the highest target MAP. This study showed that fluid resuscitation targeting a high MAP increased the mortality by accelerating the hemorrhage, while no fluid therapy at all also increased the mortality.

The same investigators also studied the effect of a more gradual increase in MAP on mortality, using the same controlled pre-bleed from the femoral artery before inducing the aortic tear.⁷ The MAP was raised to 40, 60, and 80 mmHg by normal saline infused at 6 ml/kg/min, which was later changed to blood transfusions. The mortality was 11%, 22%, and 78%, respectively. These figures corresponded to a progressive increase of the intraperitoneal hemorrhage volume, which was measured after the animals had been sacrificed. Hence, mortality was still very low when the MAP was maintained at 60 mmHg, while an abrupt increase in mortality occurred when the MAP was raised to 80 mmHg.

Sondeen *et al.*⁸ used suction of the abdominal cavity to determine the pressure at which rebleeding occurs. They found that MAP averaged 64 mmHg (systolic 94 and diastolic 45 mmHg) when rebleeding started. However, the pressure ranges were wide; for example, MAP at the onset of rebleeding varied between 30 to 90 mmHg.

Varying the infused volume

Using the aortic tear model, Bickell *et al.* studied the effects of infusing 3 times as much lactated Ringer's solution as the expected hemorrhage amount (3:1) over 10 min once the wire was pulled.⁹ Hemodynamic indices dropped markedly when the hemorrhage began, with transient improvement in response to fluid. All 8 pigs that received intravenous fluid died between 30 and 90 min after the infliction of the aortic laceration. In contrast, all 8 pigs that did not receive any fluid survived up to 120 min, when the experiment ended. Hemodynamic indices dropped markedly when the hemorrhage began, with transient improvement in response to fluid. One difference from the studies performed by Stern and Riddez was that Bickell's animals were larger, 23-40 kg versus 15-20 kg, which made the aortotomy relatively smaller in size. Moreover, the rate of infusion was higher.

In 32 of the smaller-sized pigs, Riddez and co-workers provided crystalloid fluid at a much lower rate.² The infusions were administered in volumes of 0:1, 1:1, 2:1, and 3:1 times the (here, the expected) hemorrhage per hour. The low rate of infusion of

Ringer's solution did not affect MAP but slightly increased blood flow rates in the aorta, portal vein, and left renal artery. The mortality at 2 hours was 25% in the 1:1 and 2:1 fluid groups, while being twice as high (50%) in the 0:1 and 3:1 groups.

A marked reduction of oxygen consumption appearing within the first 10 minutes predicted a poor outcome. Only four animals that developed severe early oxygen debts survived up to 2 hours, and in them, either the 1:1 or the 2:1 fluid program caused a gradual normalization of oxygen consumption. In no other animal was an early severe oxygen debt reversible, which resulted in progressive acidosis and death.

These results corroborated that infusion fluid should be provided in uncontrolled hemorrhage situations but at a lower rate and at lower volumes than indicated by the widespread practice of infusing 3 ml of Ringer's for each 1 ml of blood lost (3:1 rule).

The same group also infused Ringer's acetate in the proportion 1:1 to the hemorrhage, but only over 20 min.⁵ Hence, the infusion was provided at a rate corresponding to 3:1 per hour, but stopped much earlier. The results showed that rebleeding events occurred only during the period of time when fluid was infused. The fluid did not reverse the oxygen debt that developed early after the initial hemorrhage, and 50% of the animals subsequently died.

This study illustrated the danger of infusing fluid at a high rate rather than providing a large volume. Based on the previous work, one would expect 25% mortality to result from the infused volume, but instead, the figure found corresponded to that obtained by using the same infusion rate.² It also became even more evident that the earliest studies using the aortic tear model^{6,7,9} had infused crystalloid fluid much too fast to promote survival.

Hypertonic saline in dextran

Seven and one half percent saline in 6% dextran 70 (HSD) is a resuscitation fluid with a high potency to increase plasma volume. In humans, HSD is seven times more efficient than normal saline as a plasma volume expander¹⁰ and reverses evidence of hypovolemia very quickly in controlled hemorrhage models.¹¹ Several clinical trials have used this fluid in pre-hospital settings.^{12,13} Therefore, it was of interest to test HSD in the aortic tear model.

Bickell, Bruttig & Wade randomized 24 pigs to receive no fluid, 80 ml/kg of lactated Ringer's over 9 min, or 4 ml/kg of HSD over 1 min.¹⁴ All the control animals

survived and all the Ringer animals died. The investigators found that HSD increased the hemorrhage but not as much as Ringer's did. At 120 min, the mortality was 60%. As before, the pigs were larger than the ones used by Stern and Riddez, which meant that the 5 mm aortotomy was a less serious injury and did not necessitate fluid therapy. Halothane was used for anesthesia while Riddez used ketamine, of which the latter largely retains the cardiovascular responses typical of conscious animals.

Riddez' group performed a study comparing the outcomes of injecting HSD in the recommended dose of 4 ml/kg to the outcomes with 2/3 of the recommended dose injected over 1 min.¹⁵ The treatments rapidly restored both the aortic and splanchnic blood flows to pre-bleeding levels but less dramatically increased MAP (peak 70 mmHg). These changes were associated with re-bleeding in 80% of the pigs (Fig. 3). Sixty percent of the animals died. These results showed that effective restoration of flow parameters is not associated with good survival in this type of hemorrhage.

A later study investigated whether a slower (5 min) administration of 1 and 2 ml/kg of HSD would be better tolerated than the 4 ml/kg dose.¹⁶ The smallest volume was followed by 20% mortality while both the larger ones were associated with a mortality of 50%. The initial hemorrhage from the laceration was quite similar in the groups (approximately 400 ml in pigs weighing 21 kg), and for the most part, the animals that rebled died. Logistic regression showed that both the choice of fluid volume and the decrease in oxygen consumption after the initial hemorrhage served as predictors of death.

These three studies illustrate that HSD is dangerous to inject rapidly in the recommended dose (4 ml/kg) when there is uncontrolled hemorrhage. To promote survival, a lower dose should be chosen and the injection time should be extended. As with Ringer's,² dramatic increases in blood flow rates and rebleeding could occur without MAP being markedly changed, if at all.

Starch

Acetated or lactated Ringer's solution and HSD have long been the traditional fluids used for resuscitation in pig models of uncontrolled hemorrhage. There are scattered data on hydroxyethylstarch but no series of studies using a standardized model in which the infused volume has been varied to identify an increment that optimizes survival.

Zaar *et al.*¹⁷ used liver damage in 30-kg pigs which caused a moderately large

(200 ml) initial hemorrhage. The animals were randomized to two phases of fluid administration with equal volumes of Ringer's lactate or hydroxyethyl starch (unknown brand). The results show that Ringer's did not markedly aggravate the bleeding while it was increased 10-fold from rebleeding induced by the starch.

Alam *et al.*¹⁸ subjected pigs to femur fracture, controlled hemorrhage, and finally to liver damage. In this complex model resuscitation with 6% hetastarch (MW 600 kD, Hextend) resulted in 85% mortality while fresh whole blood, fresh frozen plasma with and without red blood cells in the ratio 1:1 were followed by 100% survival. Coagulopathy worsened after hetastarch but was reversed by all blood-based treatments.

STUDIES IN RATS

Experimental models of uncontrolled hemorrhage in rats include cutting of internal organs and blood vessels. Most widely used is the "cut tail" or "tail amputation" model which is even somewhat older than the aortic tear model.

Effect of arterial pressure

Tao Li *et al.* from China created uncontrolled hemorrhage by transecting the spleen and one branch of the splenic artery.^{19,20} Using barbitol anesthesia, their key findings with intra-abdominal hemorrhage are consistent with those found with the aortic tear model in the pig. Hence, the survival was highest when MAP was kept low (50 mmHg, while 100 mmHg is normal). A higher MAP was also associated with a progressive increase of hemorrhage volume.¹⁹ In a follow-up study, Li showed that a slightly higher MAP (70 mmHg) is optimal *after* the hemorrhage has been arrested surgically.²⁰

Anesthesia and fluid volume

By using a model of splenic injury, Abu-Hatoum *et al.*²¹ confirmed that the blood loss and the mortality increases with the amount of crystalloid fluid used for resuscitation.

Soucy, Greene, and Shires explored the "cut tail model" in a series of experiments in the 1990s which yielded results slightly different from those obtained by

the aortic tear model.²²⁻²⁴ Here, the choice of anesthesia appeared to have an impact on outcome. Ketamine, which retains vasoconstrictive responses, was associated with the highest mortality and the hypotensive anesthetic pentobarbital, which induces vasodilatation, with the lowest.²²

The group then studied conscious rats, as they hypothesized that the detrimental effects of infusion fluids found in experimental models is due to the anesthesia. Under such conditions, a larger resuscitation volume of normal saline (80 ml/kg) was followed by less hemorrhage and lower mortality (24%) than a smaller fluid volume (40 ml/kg) and no resuscitation (mortality rates were 71 and 76%, respectively).²³ The saline was infused over only 4 min starting 15 min after cutting the tail, and it did not seem to initiate rebleeding.²³ Hence, the *largest* fluid volume promoted survival.

A later study under, which was performed under ether anesthesia, compared an infusion of normal saline in a “moderate” volume of 80 ml/kg with a large volume of 283 ml/kg. Each volume group also had an arm where the fluid was infused at a low rate (3.3 ml/kg/min) and a high rate (17.8 ml/kg/min). The results showed that the rate of the hemorrhage increased with the amount of infused fluid and inversely with the rate, which is opposite to the findings with the aortic tear model. Hence, the fast infusion of the “moderate” volume was associated with the lowest mortality (40%) while no resuscitation resulted in a mortality of 83%.²⁴ Surprisingly, the hemorrhage volume in the group with the poorest outcome was only 8 ml/kg, which would not cause death in pigs or humans.

Colloids and blood products

Data on the effects of colloids and blood products in rats subjected to uncontrolled hemorrhage models begin to assemble. However, the results are difficult to interpret due to small study groups and different set-ups.

In a splenic injury model, 7.5 ml/kg/h of 6% HAES-steril (MW 200 kD) prolonged survival, but the mortality after 4 hours was still the same (75%) as for no resuscitation and for the maximum volume of Ringer’s lactate (105 ml/kg/h).²¹ The only treatment that decreased the mortality was low-volume Ringer’s lactate (35 ml/kg).

Li *et al.*²⁰ reported the better survival after splenic injury was obtained when resuscitation was performed either with a mixture of 2/3 of Ringer’s lactate and either

1/3 of hydroxyethyl starch (MW 130 kD) or whole blood as compared to when Ringer's acetate alone or hydroxyethyl starch alone was administered.

Using a liver injury model, Letourneau *et al.*²⁵ found that resuscitation with fresh thawed plasma after hemodilution was followed by 100% survival, while rats receiving thawed plasma stored for up to 5 days resulted in survival in only 54%. As all sham animals also survived, plasma appeared to exert a negative influence on survival after being stored for only a few days.

Oxygen carriers ("artificial blood") have been tested in many studies of both controlled and uncontrolled hemorrhage in pigs and rats. There is some evidence that animals receiving oxygen carriers live longer. However, none of these blood substitutes is yet generally available for clinical use.

Studies of oxygen carriers are generally hampered by lack of kinetic-derived volume matching between the oxygen carrier and the fluid used for comparison. The degree of plasma volume expansion over time is crucial to both the hemodilution and the rebleeding which, in turn, affect the oxygen transport. Improved oxygen transport and ultimately survival attributable to the oxygen carrying capacity of the fluid is difficult to demonstrate in such a complex setting.

Body temperature

The Swedish surgeon Göran Heinius found that no hemorrhage occurs when amputating the tail of a rat under hypothermic conditions. He modified the preparation by exposing the femoral artery in the groin by surgical dissection and puncturing the vessel with a 0.5 mm disposable needle. Studies under ketamine/midazolam anesthesia targeted resuscitation at out-of-hospital events in a cold climate. Rats were cooled to 30° C and subjected to hemorrhagic shock.

During fluid resuscitation, rebleeding events became more frequent, had longer durations, and contained more blood in hypothermic animals as compared to normothermic animals.²⁶ When comparing the outcomes for various fluid programs during hypothermia, the results still supported those obtained by the cut tail cut model - mortality tended to be lower in large- and moderate-volume resuscitation with Ringer's acetate solution compared to small-volume resuscitation, despite the fact that the rebleeding volume increased with the infused volume.²⁷

Hypothermia is well known to provoke coagulopathy. In white rabbits

subjected to mild hypothermia (35° C) followed by uncontrolled splenic injury, the tendency to develop coagulopathy was greater with hetastarch (MW 600 kD, Hextend) and dextran 70 compared to 5% human albumin.²⁸ Mortality rates were 100% after resuscitation with hetastarch, 75% after dextran, and 50% after albumin.

PATHOPHYSIOLOGY

Experimental studies in animals have been the key source to our understanding of the balance between beneficial and adverse effects of fluid infusion in uncontrolled hemorrhage. Injury to a large blood vessel results in the formation of a thrombus that adheres to the outer surface of the vessel and the surrounding tissue.^{29,30} In pigs, this immature clot arrests the hemorrhage within 4 min in the aorta,^{4,5,15,16} while liver injury might require twice as long time.³¹ However, mechanical and chemical forces can apparently disturb stabilization of the clot.

A rise in the arterial pressure dilates the vessels and might wash away the thrombus by sheer force, which initiates rebleeding both in the aortic tear model^{6,7} and in the femoral artery model^{32,33} of swine. Monitoring of rebleeding events by the double flow probe method shows that an increase in blood flow rate, which increases the kinetic energy,³⁴ is a more sensitive marker of rebleeding than MAP.

For example, cardiac output increased by 60% during the 10 min just prior to a major rebleeding event in 4 pigs, and cardiac output was already above baseline in a fifth animal. At the same time the aortic blood flow increased by 40% on the average. In contrast, the systolic arterial pressure rose by only 2 mmHg (to 58 mmHg) and MAP remained unchanged (32 mmHg, unpublished).²

Hence, an increase in blood flow typically precedes a rebleeding event, which suddenly reduces the resistance to flow, and thereby, further but transiently increases the flow rate¹⁶ (Fig. 3). When a new clot forms, the blood flow rate again decreases. Hence, the blood flow in a vessel and the hemorrhage exhibit a timely interplay. Another factor that might contribute to rebleeding is the reduced viscosity that results from the hemodilution induced by infusion fluids.

The incidence of rebleeding is very low when crystalloid fluid therapy is not actively performed. On the other hand, some fluid should apparently be infused to

prevent hypovolemic shock,^{2,22} recognizing that vigorous fluid administration is detrimental in the intra-abdominal hemorrhage, both when resuscitation is performed with isotonic^{9,19} or hypertonic fluid.¹⁴⁻¹⁶ In contrast, vigorous fluid administration (80 ml/kg) promotes survival in the cut tail model, which represents a more peripheral vascular injury, although the hemorrhage volume might be larger.²²⁻²⁴

Ambitious fluid therapy may not be as deleterious in uncontrolled hemorrhage from parenchymal organs. For example, in a model of liver injury in the rat, hypertonic saline maintained circulating blood volume and survival despite increased hemorrhage.³⁵ In the pig, administration of 4 ml/kg of HSD did not induce rebleeding from a liver injury.³¹ However, uncontrolled hemorrhage from parenchymal organs has been less intensively studied than direct injuries to major blood vessels.

IMPLICATIONS FOR TREATMENT

Clinical studies

The ultimate treatment of major hemorrhage is surgical, but in anesthesia and trauma care there is a reflex behavior based on the belief that fluid should be infused to “buy time” before irreversible shock develops. The possibility that uncontrolled hemorrhage from a major blood vessel might be present makes this therapy potentially dangerous. The prevalence of the uncontrolled type of hemorrhage in pre-hospital settings is unknown, but one author estimated the incidence to be 25% of blunt traumas to the chest, abdomen, or pelvis.³⁶ In penetrating trauma, the incidence is probably higher.

In a classical study of pre-hospital penetrating injuries, Bickell and co-workers in 1994 compared the outcomes of 598 hypotensive patients half of which received infusion fluid on the scene of an accident while the other half received fluid only after having entered the operating room.³⁷ The immediate-resuscitation group received 2.5 L of fluid and the delayed resuscitation group only 350 ml before entering surgery. The results showed a slight but statistically significant increased survival rate in the delayed resuscitation group (70% versus 62%). Differences were greater in the most severely

injured patients (61% versus 48%). This study appears to support the “scoop-and-run” strategy in hypotensive trauma patients in large cities when the transport time to hospital is no longer than 20-30 min. In rural areas, where transport time exceeds 30 min, hypovolemic shock should probably be treated with infusion fluids on the scene of the accident and during transport to hospital.

The value of HSD in the pre-hospital setting has been the subject of many studies. Eight clinical trials in the 1980s and 1990s failed to show an effect on survival. A meta-analysis based on 6 of the 8 trials still showed a mortality rate of 23.8% in those patients treated with isotonic fluid and 17.3% in those who received HSD as a first treatment, a difference that was statistically significant.^{12,38}

The Canadian surgeon Eileen Bulger has more recently re-assessed HSD in several clinical trials comprising over 800 patients. She found that neither mortality nor the neurological outcome in trauma victims differed between the administration of HSD, 7.5% saline, and the use of normal saline, which was the standard of care.^{13,39} However, the dose of HSD in the study was 250 ml, which corresponded to the 4 ml/kg shown to be detrimental in the aortic tear model.¹⁴⁻¹⁶ Hence, the fluid therapy might have brought the patients from lower to the upper part of the U shaped mortality *versus* amount of fluid curve, then passing the increment where survival is optimal.

Some encouraging results with hydroxyethyl starch as first-line treatment in trauma have been reported^{40,41} while a colloid/crystalloid ratio >2 seems to promote coagulopathy.⁴² A problem is that most studies involving starch use hetastarch (MW 600 kD, Hextend) which has very limited role in European medical care.

Hemostatic dressings and drugs

Animal studies of uncontrolled hemorrhage have recently focused on ways to decrease and control the bleed volume with mechanical devices and hemostatic drugs. For example, the femoral artery in pigs has been used to study the patency of wound dressings to withstand increasing arterial pressures.^{32,33,43}

Tranexamic acid, which inhibits fibrinolysis, had no effect on the amount of blood lost in the aortic tear model in the pig when administered between the time of the initial hemorrhage and the initiation of fluid resuscitation.⁴⁴ Other studies have dealt with desmopressin, which increases the concentration of the von Willebrand factor and coagulation factor VIII and improves platelet adhesion to injured endothelium. An

aortic tear model in rabbits showed that both permissive hypotension and desmopressin augments clot formation; however, the desmopressin was then administered 1 hour before hypovolemic shock was induced.⁴⁵ In the cut tail model of the rat, neither tranexamic acid nor desmopressin had such an effect when given approximately 5 min before hemorrhage was induced.⁴⁶ In addition, desmopressin did not alleviate hemorrhage in the femoral artery model of hypothermic rats; here, the drug was injected 5 min after hypovolemic hypotension had been induced.²⁷

Recombinant-activated factor VII (rFVIIa; NovoSeven) has received the greatest attention among the hemostatic drugs. Several animal studies and smaller clinical trials of this procoagulant therapy have been published in the past decade.⁴⁷ However, these studies do not challenge fluid therapy and, therefore, are outside the scope of this review.

Volume kinetic analyses

Computer simulations based on volume kinetic data derived from humans corroborate many experiences from animal experiments. Such simulations show that the resuscitation strategies practiced for decades are likely to boost the blood flow rates by increasing the blood volume to supramaximal levels, thereby promoting rebleeding.

Crystalloid fluids. An often overlooked fact is that distribution of crystalloid fluid from the intra- to the extravascular space is not immediate. The distribution half-life averages 8 min, which makes Ringer's solution a more effective plasma volume expander than commonly believed as long as the fluid is infused and for 20-30 min thereafter⁴⁸ (Fig. 4).

Simulations based on data from Drobin & Hahn⁴⁹ illustrate the summary effect of distribution and capillary refill on the plasma volume expansion in normotensive adult male volunteers who had 900 ml of blood removed within 10-15 min (controlled hemorrhage). Here, the practice of infusing 3 times the hemorrhage volume with Ringer's solution (3:1 rule) over 30 minutes is shown to create marked hypervolemia (Fig. 5A). The infusion volume required to restore normovolemia is rather 1.5 L (1.6 times the bled volume) if fluid resuscitation starts immediately after the hemorrhage. The required volume will be only 1.0 L if the infusion is initiated with a delay of 45 min (Fig. 5B).

A nomogram, depicting the infusion rates and infusion times required to restore

the blood volume after hemorrhage of 450 and 900 ml, is shown in Fig. 6. Isobars also indicate how deliberate hypovolemia (-300 ml), which appears to be justified to prevent both shock and rebleeding, can be achieved. The nomogram is based on a time lapse of 30 min between the hemorrhage and the initiation of fluid resuscitation, which is representative for many pre-hospital scenarios.

If bleeding continues, further computer simulation yields that the requirement for maintaining deliberate hypovolemia (-300 ml) is to infuse 1.6 times the continuously bled volume with Ringer's acetate, which must be increased to 2.0 times the bled volume if normovolemia is desired. These ratios probably become altered with time as the intravascular space gradually becomes depleted of proteins. Data for further simulation is not available, but blood products become critically needed to prevent coagulopathy and to maintain oxygen delivery when approximately one blood volume has been replaced in this way. If available, they should naturally be transfused at much earlier stage of a serious hemorrhage episode.

Another volunteer study confirms that infusing 900 ml of Ringer's after withdrawal of 900 ml of blood creates a slightly hypokinetic circulation, while 1800 ml is followed by a clear hyperkinetic circulation with increased lung water.⁵⁰ The authors concluded that optimal volume substitution with Ringer's is obtained by infusing between 100% and 200% of the blood lost.

Studies in humans undergoing surgery⁵¹ and bled pigs¹⁷ also support that the immediate plasma volume expansion from Ringer's solution is 60-75% of the infused volume, which is much greater than proposed in medical textbooks.

Little is known about the disposition of infusion fluids in hypovolemic hypotensive states. Retrospective analysis of animals *without* rebleeding from two pig studies^{2,5} suggest that the fluid efficiency of Ringer's acetate solution over 20, 30 and 50 minutes is similar to those shown for normotensive humans in Figure 5 (for calculations, see Appendix). An exception might be that the distribution could occur more slowly during onset of the hypotension, as is the case during induction of anesthesia.⁴⁸

Hypertonic and colloid fluids. Volume kinetic studies of HSD have only been performed in normovolemic volunteers¹⁰ and sheep.⁵² Hypervolemia of at least 400 ml can be expected if 250 ml (approximately 4 ml/kg) of HSD is infused over 10 min after a hemorrhage of 900 ml (simulation not shown). The dose of HSD that fully restores the

blood volume is rather 150 ml (approximately 2 ml/kg) than 250 ml. Retrospective analysis of 11 pigs with hypovolemic hypotension but without rebleeding¹⁶ indicates that a low MAP does not markedly change the efficiency of HSD to expand the plasma volume.

There are no volume kinetic data on isotonic colloid fluids or blood products in hypovolemic states that allow construction of infusion rate/time-plots, as is possible for Ringer's acetate (Fig. 6). Moreover, the existing studies have not varied the infusion volume or infusion rate in a way that allows us to even extrapolate a dosage that would prevent shock but still avoid rebleeding. Such data would be very helpful for those who wish to manage uncontrolled hemorrhage with fluids other than Ringer's or HSD.

This issue might still be less crucial for colloids than for crystalloids as these fluids lack a prominent distribution phase.⁴⁸ There is reason to believe that less volume should be infused in uncontrolled hemorrhage than commonly believed, as catecholamine secretion and capillary refill in response to the hemorrhage promote a hyperkinetic circulation and partly restore the blood volume.

Scattered experimental evidence support this view. For example, infusion of 900 ml of 5% albumin after withdrawal of 900 ml of blood in volunteers increased cardiac output to 400 ml/min and the blood volume to 200 ml above baseline⁵⁰ while 5% albumin is known to expand the plasma volume by 80% of the infused amount in normovolemic volunteers.⁵³

Rational basis of treatment

The experience from studies in pigs and most data from rats, the exception being those derived by the cut tail model, show that a normal arterial pressure and high blood flow rates should be avoided. The arterial pressure can be monitored while the blood flow in a major vessel is more difficult to assess. However, high flow rates are primarily a consequence of the intravenous fluid therapy. Our best way to avoid them is currently to adopt a well-tailored fluid therapy program.

The clinically adopted rule is to avoid restoring MAP to normal levels. A current guideline suggests that target MAP that assures optimal survival probably is 65-75 mmHg (systolic pressure 80-100).⁵⁴ A recommendation of a MAP of 60 mmHg has previously been given based on data from pigs.⁸ Such "permissive resuscitation" includes restrictive fluid therapy, with the possible addition of vasoconstrictive drugs in

case MAP is too low to permit essential tissue perfusion. Unfortunately, the benefit of permissive resuscitation has not been convincingly demonstrated in human trauma situations. In any event, the practice should be abandoned to secure cerebral perfusion in case of concomitant head trauma.

Restoration of blood flow rates by infusion fluids should avoid hypervolemia. As already shown, replacing blood loss by 3 times the volume by Ringer's or 250 ml of HSD causes hypervolemia in volunteer experiments and might be deleterious when there is a risk of rebleeding. Volume kinetics also suggests that bolus infusions of crystalloid fluid should *not* be used, as the distribution effect will create marked but transient changes in blood volume (Fig. 4). An oscillating pattern of blood volume changes is less likely to occur from HSD or colloid boluses, as these fluids lack distribution function.⁴⁸

The effects of the resuscitation with fluid and drugs should be observed closely.⁵⁵ Animal experiments hold that a typical sign of rebleeding is a sudden drop in arterial pressure when fluid administration is considered adequate. If this occurs the intensity of the fluid resuscitation should be reduced, not increased. A risk with using the "target MAP" strategy is that more fluid would be infused in such a situation, which will only aggravate the rebleeding problem. In addition to the arterial pressure, patient monitoring includes plasma lactate and acid-base balance.⁵⁴ Arterial samples are preferred. Progressive acidosis indicates bad prognosis.^{2,15} A low oxygen consumption precedes the development of acidosis, but this measurement is not clinically available.

What volumes and infusion rates can then be recommended? No absolute truth can yet be presented, although we are aware of what should be avoided. The amount of blood lost is usually unknown, but one may take a blood loss of 1,000 ml as an initial assumption when hemorrhage has resulted in arterial hypotension in an adult man. The starting volume of Ringer's could well be 600-750 ml over 20-30 min, after which the patient would still be somewhat hypovolemic (Fig. 6). Both animal experiments and kinetic simulations suggest that a reasonably safe initial fluid resuscitation with HSD should consist of 100 ml over 5-10 minutes. Extending the infusion time to 20 min is likely to further increase the safety of this treatment.

These implications given above should not be regarded as clinical guidelines but as rational conclusions based on the experiments referred to in this review.

Colloid fluids still have a limited place for first-line resuscitation in trauma.⁵⁸

Fresh whole blood and plasma are most likely superior to clear fluids,⁵⁵ provided that they are not given in amounts large enough to cause rebleeding. However, logistic problems rarely make blood-based fluids available before the patient reaches a trauma center or university hospital. At that time, uncontrolled hemorrhage can be diagnosed by surgical exploration or invasive radiology. Definite treatment is surgical.

Many recent studies deal with retrospective analyses of survival depending on how various blood products have been combined. These studies, which are boosted by experiences from the wars in Iraq and Afghanistan, associate improved outcome with earlier use of plasma and platelets.⁵⁹ However, these exciting topics, as well as many other in essential components of trauma care, fall outside this review.

CONCLUSIONS

Uncontrolled hemorrhage occurs from damage to major blood vessels. The bleeding stops spontaneously when blood flow rates and MAP decrease as part of hypovolemic shock. Experimental studies in animals demonstrate that stabilization of the clot can be disturbed by a rise in blood flow rate and/or MAP. Such changes promote rebleeding, which markedly increases the size of the total hemorrhage as well as the resulting mortality. Rebleeding events become more frequent and longer when complicated by hypothermia, which gives rise to both vasoconstriction and coagulopathy. Rebleeding probably becomes less of an issue in distal vascular injuries.

To avoid rebleeding and to assure optimal survival, a resuscitation program that does not aim to restore normal MAP (“permissive hypotension”) should be used. A rise in blood flow rate augmented by an increased blood volume appears to be an earlier sign of improved hemodynamics than MAP. The blood flow rate is primarily governed by the plasma volume expansion caused by intravenous fluid.

The mortality versus the amount of fluid curve shows a U shaped curve with higher mortality at either end. No fluid at all allows hypovolemic shock to become manifest and too much fluid promotes further exsanguination. Unfortunately, traditional clinical rules of volume replacement tend to place patients on the upper part of the U-shaped mortality curve. Animal experiments and computer simulations based on fluid volume kinetics suggest that initial fluid resuscitation in a hypotensive patient may

consist of 600-750 ml of crystalloid fluid or 100 ml of HSD. Fluid and drugs should be titrated and the effects be observed closely.

There is considerable difficulty in making the diagnosis of rebleeding, especially under pre-hospital conditions, but a typical sign is a sudden drop in arterial pressure when fluid administration is considered adequate.

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Appendix

Fluid efficiency is the fraction of infused fluid that is retained in the bloodstream. A simplified expression can be obtained from the change in blood hemoglobin (Hb)

concentration from just before to the end of an infusion. In pigs, we assume that the blood volume at baseline (BV_o) is 7% of the body weight. The change in blood volume is then obtained from before (Hb_o) and after (Hb_t) the infusion:⁶⁰

$$\Delta BV = BV_o(Hb_o / Hb_t) - BV_o$$

The amount of fluid retained in the blood is then given by:

$$\text{Fluid efficiency (\%)} = 100 * \Delta BV / \text{infused volume}$$

With the double flow probe method the initial hemorrhage volume can be calculated and should be subtracted from BV_o . Thereafter, the capillary refill occurring before fluid therapy starts is accounted for by the Hb change as indicated above.

These calculations need to be performed differently if hemorrhage occurs during the actual infusion.⁶¹

Fluid efficiency is time-dependent, as apparent from Fig. 4B. This problem can be overcome by volume kinetic methods, which require serial sampling of Hb.⁴⁸ Calculations either compare fluids with respect to the area under the plasma dilution-time curve following a standard infusion, or else contrast computer simulations based on differential equations.¹⁰

Legends for figures

Fig. 1 Principle of the double flow probe method of monitoring aortic hemorrhage in the pig. When the steel wire makes the lesion, the rate of the hemorrhage is the difference in flow between the two aortic probes. Drawing by Dr. Louis Riddez.

Fig. 2 Blood flow rates over 4 min measured at the sites shown in Figure 1 when pulling the steel wire affixed to the wall of the aorta induces uncontrolled hemorrhage. Data from Reference 4.

Fig. 3 Typical flow changes in the proximal aorta that initiates rebleeding in a pig with aortotomy at 0 min. Fluid therapy with 7.5% saline in 6% dextran 70 (HSD) increases the blood flow rate, which is boosted by the decreased resistance to flow caused by the opening of the vessel when rebleeding occurs. Based on data from Reference 16.

Fig. 4 Plasma volume expansion during and after infusing 2.7 L of Ringer's acetate solution over 30 minutes in an average normovolemic adult volunteer weighing 76 kg (A). The fraction of the infused fluid that remains in the blood at any given moment (B). Simulations based on kinetic data from 8 volunteers published in Reference 49.

Fig. 5 Plasma volume relative to baseline when Ringer's acetate solution is infused according to the 3:1 rule over 30 minutes after 900 ml of blood has been withdrawn from male volunteers weighing 76 kg (A). To reach normovolemia a much smaller amount of Ringer should be infused. Titration is necessary to maintain normovolemia (B). Simulations based on kinetic data from 10 volunteers published in Reference 49. Capillary refill is estimated according to References 56 and 57.

Fig. 6 The infusion rate and infusion time of Ringer's acetate required to restore the blood volume to normal and to modest hypovolemia of 300 ml after withdrawal of 450 ml of blood **(A)** and 900 ml of blood **(B)** in adult male volunteers weighing 76 kg. Infusion began 30 min after the end of rapid blood withdrawal. Computer simulations based on kinetic data from Reference 49. Capillary refill was estimated to be 150 and 300 ml, respectively.

Fig. 1

Fig. 2

Fig. 3

Fig. 4

Fig. 5

Fig. 6