Notes on Hemostatic Resuscitation

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We learned in residency that the treatment for hemorrhagic shock is Volume, Volume, and more Volume. But is this really true?

Introduction: Why we like fluids.

The concept of giving fluids as a treatment for hemorrhage is obvious, especially when blood loss is readily visible. If the body loses fluid it makes sense to replace it. Classic war movies portray the wounded soldier as thirsty, with the compassionate medic giving water to ease the distress. Modern TV shows emphasize “1 liter of normal saline, STAT.” And indeed, few therapies are so immediately gratifying. In a fluid depleted, vasoconstricted patient, administration of an intravenous fluid bolus predictably increases myocardial wall tension, resulting (through Starling’s law) in increased contractility and thus increased blood pressure. The thing we measure (blood pressure) responds immediately to the thing we do (give fluids). This makes us feel better, and in control.

Further, there is a wealth of research demonstrating the value of fluid therapy when the body is hypovolemic. The modern era of resuscitation science began with development of the Wiggers model of controlled hypotension in the 1950s, followed by the work of Shires a decade later. Bleeding was found to produce consistent organ system hypoperfusion, which led to a variety of bad outcomes, including mortality. Ischemic animals benefitted from fluid therapy: tissue perfusion improved, and morbidity and mortality were reduced. Even within the past few years, this concept has been further hammered home. Blow et al demonstrated worse outcomes in the ICU if “occult hypoperfusion” in trauma patients was not recognized and addressed, while Rivers and colleagues showed the benefit of “Early Goal Directed Therapy—“ a thinly veiled excuse for greater fluid administration—in patients presenting to the Emergency Department in septic shock.

Within anesthesia the concept of treating hypoperfusion with fluids is a cornerstone of residency training. We know how much anesthesia the patient needs—1 MAC, right?—so if they’re hypotensive it must be because they’re hypovolemic. Failure to give fluids will lead to postoperative visual loss (maybe), acute renal failure (maybe) and the twin boogeymen called stroke and MI. Yet the data does not support these fears. Deliberate hypotension during anesthesia has been studied many, many times and generally found to be safe. And all of us have seen patients with mean arterial pressure as low as 40 mmHg who woke up just fine. In fact, absent patients who need CPR, ischemic injury is vanishingly rare.
Risks of Fluid Administration

But why not give the fluid? Where’s the harm in it? Not surprisingly, there are risks as well as benefits to fluid administration. The first is increased bleeding. Any elevation of blood pressure will increase bleeding from open vessels and will tend to wash away clots that have already formed. In the vasoconstricted shock patient even small boluses of fluid can produce sharp increases in pressure and subsequent rebleeding. And in the case of new tissue injury (i.e. surgery), the higher the blood pressure, the more blood will be lost and the harder the bleeding will be to control.6

Further is the issue of blood dilution. Crystalloid or colloid fluids will dilute native clotting factors and red cell mass. While red cell dilution will not decrease oxygen delivery, it will increase the rate of tissue bleeding through a decrease in viscosity and a loss of red cell facilitation of clotting. It is well established (although little known) that clotting occurs more rapidly at a higher hematocrit.7 Plasma dilution also lowers the concentration of soluble clotting factors and platelets at the site of bleeding, leading to slower and less solid clot formation. While the body has some capacity to respond by releasing stored factors, this capacity is limited and rapidly overwhelmed by trauma or major surgery.

Finally, it is clear that the fluids we commonly use are not as benign as we would like. Both crystalloid and colloid fluids have immune-mediating effects, usually suppressive.8 Fluid therapy just by itself can damage vascular endothelium and lead to increased permeability.9 Unless carefully managed, fluid administration will also make the patient colder, further contributing to both coagulopathy and immune suppression.

Animal Studies of Fluid Restriction

Although identified repeatedly during wartime surgery (all the way back to World War I), the concept of deliberate hypotension during active bleeding has been slow to sink in. In 1964 Shaftan published a study of coagulation in dogs, demonstrating that it is formation of a soft extraluminal clot that limits bleeding following arterial trauma.10 This study compared blood loss from a standard arterial injury under various conditions. The least blood loss occurred in hypotensive animals (whether hypotensive from hemorrhage or from vasodilator administration), followed by controls, followed by vasoconstricted animals. Greatest blood loss occurred in animals that received vigorous fluid reinfusion during hemorrhage.

A series of reports in swine, rats, sheep and dogs established that, while some resuscitation was needed to prevent early death from exsanguination, the optimal target systolic pressure for best survival was in the range of 70-80 mmHg.11-15 Attempts to normalize systolic pressure prior to anatomic control of hemorrhage lead to rebleeding, increased requirement for resuscitation, increased blood loss, and increased mortality.
In the most sophisticated models, direct assessment of cardiac output and regional perfusion show no difference between moderate or large volume resuscitation in cardiac output, blood pressure, or regional perfusion of the heart, kidneys, and intestines. Burris studied both conventional resuscitation fluids and various combinations of hypertonic saline and dextran, finding that rebleeding was correlated with higher mean arterial pressure (MAP), and survival was best in groups resuscitated to lower than normal MAP. A 1994 consensus panel on resuscitation from hemorrhagic shock noted that mammalian species are capable of sustaining MAP as low as 40 mmHg for periods as long as 2 hours without deleterious effects. The panel concluded that spontaneous hemostasis and long-term survival were maximized by reduced administration of resuscitation fluids during the period of active bleeding, seeking to keep perfusion only just above the threshold for ischemia.

**Human Trials of Deliberate Hypotensive Resuscitation**

Two large trials of deliberate hypotensive resuscitation have been conducted in trauma patients. The first, in Houston in the early 1990s, randomized hypotensive victims of penetrating torso trauma to conventional management or to no intravenous fluid during prehospital and ED care. This trial demonstrated a significant improvement in outcome (62% vs. 70% mortality) with fluid restriction, but was controversial because of its focus on penetrating trauma only, its failure to continue fluid restriction into the early operative period, and its “all or none” methodology. Following this, a retrospective review of resuscitation strategy in a large population of hemorrhagic shock patients demonstrated increased mortality when a rapid infusion system was used. A second prospective trial enrolled both blunt and penetrating trauma patients at the time of hospital arrival, and randomized fluid therapy to target a systolic pressure of either 80 mmHg or 100+ mmHg. There was no difference in mortality between groups, although the overall mortality (8%) was much lower than in the earlier trial due to the exclusion of moribund patients.

Although not of themselves perfect evidence, these trials were convincing enough regarding the safety and potential benefit of deliberate hypotension that this approach has become the recommended policy in most major trauma centers. Even so, fluid restriction requires very close attention to detail in the ED, and a willingness to tolerate systolic blood pressures of 80-90 mmHg. This kind of discipline is rare, and it is likely that most bleeding patients, in most settings, still receive too much crystalloid fluid.

**New Thinking about Fluid Resuscitation**

In the new millennium thinking about resuscitation has evolved even further, in an effort to reduce the long-term harms from hypoperfusion while maintaining the hemostatic benefits of keeping the blood pressure low. With the recognition that the coagulopathy of trauma is caused not just by dilution, hypothermia and acidosis (the so-called ‘lethal triad’) but also by an acute inflammatory response to tissue injury, there has been
increasing focus on early support of the coagulation system. Several large retrospective series in both military and civilian trauma have demonstrated improved outcomes when plasma and platelets are given earlier, and in greater quantities.\textsuperscript{23-27} Although not yet demonstrated in a prospective trial, these observations have led to the recommendation of empiric 1:1:1 RBC:plasma:platelet administration (instead of crystalloids or colloids) as the indicated fluid therapy for hemodynamically unstable patients with ongoing bleeding. Uncrossmatched type-O RBC have been used by major trauma centers for many years, and have a superior safety record.\textsuperscript{28,29} In the past few years large centers have also begun using prethawed or liquid universal donor (type AB) plasma early in resuscitation.

Using a whole blood mix as the resuscitation fluid for hemorrhaging patients largely avoids the issue of dilution, but what about concern for hypoperfusion? Postulated as beneficial, but not yet studied even retrospectively, is the aggressive use of anesthetic agents early in resuscitation. In theory, this approach would reverse vasoconstriction and improve perfusion while maintaining low blood pressure during the period of active hemorrhage. Rather than maintaining hypotension by fluid restriction, this approach accomplishes it by vasodilatation. The downside to this approach—the risk of complete circulatory failure caused by administering anesthetics to a patient in shock—requires careful management. In the early going, titration of small doses of anesthesia (usually fentanyl) are balanced by small boluses of fluid (1:1:1 blood products) until an adequate anesthetic state is achieved. In the face of the dynamic changes produced by injury and surgery, this requires excellent intravenous access, an efficient rapid infusion system, close monitoring of blood pressure, and an experienced provider. When successful, the result is a stable, vasodilated physiology that keeps blood pressure low, blood composition close to normal, and the circulation largely intact.

**Hemostatic Resuscitation: Validation**

Validation of these theories in randomized controlled clinical trials is lacking, but support at a lesser standard of evidence has come from the military experience in Iraq and Afghanistan. Several retrospective studies of massively transfused casualties have demonstrated that earlier and more aggressive administration of plasma and platelets during uncontrolled hemorrhagic shock appears to improve outcomes. These analyses are strongly confounded by the logistics of blood transfusion (i.e. the rate at which blood products of various types can be made to arrive at the bedside) and the survival bias which results. In some studies improved survival with early use of plasma is really reflecting a slower rate of hemorrhage, which allows the patient to live long enough for plasma to be transfused. Nonetheless, striving for 1:1:1 resuscitation is physiologically appealing in the patient where the duration of hemorrhage is unknown. A summary of the dozens of papers which have appeared on this topic in the past few years concluded that early administration of clotting factors is likely beneficial, but that the effect may be hard to demonstrate in routine clinical practice.\textsuperscript{30}
Summary and Recommendations

Based on the evidence presented, the following is this author’s recommended approach to early resuscitation—while the patient is still actively bleeding—following traumatic injury or major surgical misadventure:

- Maintain systolic blood pressure 80 – 100 mmHg
- Maintain functional blood composition, using empiric 1:1:1 transfusion therapy
- Maintain normal serum ionized calcium
- Maintain core temperature > 35 degrees C
- Follow base deficit and serum lactate as markers for hypoperfusion
- Transition the patient to deep anesthesia

References

29. Camp FR, Conte NF, Brewer JR: Military blood banking, 1941-1973: Lessons learned applicable to civil disasters and other considerations; a monograph. Fort Knox, KY, U.S. Army Medical Research Laboratory, 1973