Endpoints for Fluid Resuscitation in Hemorrhagic Shock

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Vigorous intravenous fluid resuscitation has become widely accepted as the optimum management of hemorrhagic shock in trauma. There is now, however, sufficient evidence for this position to be reviewed. Hypotensive or delayed resuscitation has been postulated as a means by which the mortality associated with treatment can be reduced. It has been suggested that overresuscitation with intravenous fluids may worsen hemorrhage. This article discusses the possible adverse effects of "conventional" resuscitation and examines the evidence to support alternative treatment modalities.

Key Words: **Fluid resuscitation, Hemorrhagic shock, Trauma.**

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Shock is a pathophysiologic state in which the circulatory system is unable to perfuse tissues and meet oxygen demand adequately. Uncorrected, it leads to end-organ hypofunction, then permanent organ damage, and ultimately organ failure. Reversal of shock can take place in two ways: physiologic compensation or medical intervention. Any potential treatment should be evaluated carefully to ensure that any possible detrimental effects on homeostasis and repair processes are minimized.

In hemorrhagic shock, the main management strategies are the arrest of bleeding and the replacement of circulating volume. During much of the second half of the twentieth century, aggressive fluid administration was encouraged.[1,2] Over the last decade, however, this approach has been reexamined.[3] Intravenous fluids appear to improve hemodynamic indices in the short term, but most also have adverse consequences on hemostatic mechanisms[4] that may result in exacerbation of blood loss.[5–7] Specifically, bleeding may be exacerbated by injudicious fluid administration as a consequence of a dilutional coagulopathy and secondary clot disruption from increased blood flow, increased perfusion pressure, and decreased blood viscosity. It has also been suggested that inappropriate attempts at intravenous cannulation may lengthen on-scene times, leading to hypothermia and increased mortality because of delays in achieving definitive care. Both the volume that is administered and its timing in relation to definitive hemostasis will affect the balance of risks associated with fluid management.

The key objective is to find ways in which circulation can be supported adequately to allow vital organ preservation while keeping the risk of further bleeding as low as possible. One way of achieving this compromise is the use of so-called hypotensive resuscitation. This article examines the evidence relating to hypotensive resuscitation regimens and how they can be applied in the shocked trauma patient.

HYPOTENSIVE RESUSCITATION METHODS

Controlled intraoperative hypotension is a well-established and widely used concept in anesthesia.[8] On occasion, pharmacologic intervention is used to reduce blood pressure before surgery, as, for example, in the preoperative management of aortic dissection or contained aortic rupture. There are two possible strategies in trauma: delayed resuscitation, where fluid is withheld until hemostasis is definitively achieved; and permissive hypotension, when fluid is given but the endpoint for resuscitation is lower than normotension.[9]

In clinical practice, approaches can be combined and tailored to individual need, so that the differences between regimens are not always clearly defined. Similarly, in both animal and human studies, the boundaries between these approaches are often indistinct. Consideration of the limited evidence currently available, however, allows inferences to be drawn regarding the safety of fluid resuscitation and recommendations to be made regarding optimal intervention in the shocked patient.

EVIDENCE FROM HUMAN STUDIES

There are few randomized, controlled studies to draw on. The landmark article by Bickell et al. provides a basis for examining hypotensive resuscitation.[10,11] This was a single-center, prospective, randomized, controlled trial carried out in Houston between 1989 and 1992. The subjects were 598 adult trauma victims with penetrating torso injury and a systolic blood pressure of less than 90 mm Hg at presentation. Patients were assigned into an immediate fluid group, receiving "standard fluid therapy" (immediate resuscitation [IR], n = 238), and a delayed resuscitation (DR) group (n = 289) of patients who were cannulated but who did not receive fluid until they reached the operating theater. The predominant resuscitation fluid was Ringer's lactate. Patients in the IR group received, on average, 870 mL before reaching the

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hospital and 1,608 mL in the emergency department, whereas patients in the DR group received 92 and 283 mL at the corresponding stages. Systolic blood pressure was higher in the IR group on arrival at the trauma center (79 mm Hg vs. 72 mm Hg, $p = 0.02$). However, hemoglobin and platelet count were lower and there were increases in prothrombin and partial thromboplastin times compared with the delayed group. Furthermore, the apparent hemodynamic improvement on arrival was not sustained to arrival in theater, and there were no significant differences in transfusion requirements at operation. In the DR group, survival was better (70% vs. 62%, $p = 0.04$) and in-hospital stay for survivors was shorter. The findings suggested that for hypotensive patients with penetrating injuries of the chest and abdomen, deferring fluid administration improves outcome. The authors are careful to point out that their population was predominantly young (mean age, 31 years) and the urban setting implies relatively short transfer times. There have also been cautionary comments from Jacobs, Siegel, and others.[12,13] Questions were raised about methods of randomization, timing of mortality (the differences appear not to be significant when divided into preoperative and intra- or postoperative deaths) and the significance of delaying resuscitation given that the times to operative intervention were short. The most important caveat is that this article looked only at the victims of penetrating trauma. Although the relevance of the article by Bickell et al. is clear, it leaves questions regarding the best approach to managing blunt trauma victims, elderly trauma victims, and patients with concurrent head injury unanswered.

In the United Kingdom, a randomized controlled study was carried out to address the issue of fluid resuscitation in blunt trauma.[14] Paramedics were divided into two groups giving either immediate fluids (IR) or no prehospital fluids (DR). The crews swapped protocols at the midpoint of the trial; 1,309 patients were recruited (IR, 699; DR, 610). No major differences were found between the patient groupings in terms of mortality, complications, or health status on follow-up questionnaire. It is not possible to draw safe conclusions from this work, however, because of poor protocol compliance resulting in only 31% of the IR group receiving fluids, whereas 20% of the DR group also received fluid.

There is further evidence from retrospective work. Sampalis et al.[15] reviewed the outcomes of 217 trauma victims who had received intravenous therapy and compared them with 217 controls who had received no fluids. Correction was made for age, gender, mechanism of injury, and Injury Severity Score (ISS). Sampalis et al. found that on-site fluid administration was associated with a higher mortality, particularly in those patients with longer prehospital times. Hambly and Dutton[16] retrospectively matched patients who were given fluids using a rapid infusion system with historical controls who had undergone standard resuscitation. The use of rapid infusion was associated with a higher mortality. The results also suggested that this difference was apparent in blunt and penetrating trauma. Dunham et al.[17] had compared rapid small-volume infusion with slower large-volume infusion. In a prospective study of 36 hypotensive trauma patients during the first 24 hours of admission, they found that fluid requirements were lower and that acidosis and coagulopathy were less marked when rapid infusion of lower volumes were used.

There are some studies suggesting that it is an increase in blood pressure, before definitive hemostasis has been achieved, that is detrimental, adding weight to the theory that aggressive fluid resuscitation risks exacerbating hypovolemia by precipitating rebleeding. Dickinson and Roberts[18] found in a meta-analysis that intensive care stay was longer after the use of military antishock trousers. Spaite et al.[19] reported that an increase in blood pressure was seen in 91% of patients who died unexpectedly during prehospital transfer after trauma.

Some further indirect corroboration can be found. Several authors have scrutinized the effectiveness of paramedics in the prehospital setting.[20] Demetriades et al.[21] compared the outcome of trauma patients who were transported by paramedic crews (n = 4,856) to the outcome of patients who were brought in by others such as bystanders and nonmedical professionals (n = 926). They suggest two possible reasons for the poorer outcomes seen in the paramedic group once ISS and confounding variables had been accounted for. First, increased duration of transfer to hospital, allowing for time for emergency call, response time, on-scene time, and transfer time. Second, they question the interventions carried out by paramedics, including the use of intravenous fluids.

There are also data concerning the use of hypotensive strategies in similar but nontraumatic hypovolemic settings. Blair et al.[22] studied early versus delayed transfusion in 50 patients with gastrointestinal hemorrhage and found that rebleeding was increased in the early transfusion group. Crawford[23] similarly advocates hypotensive resuscitation in the management of leaking abdominal aortic aneurysm.

Evidence relating to demographic subgroups within the trauma population is more limited. It is believed that the elderly tolerate hypotension less well than younger people.[24] Tornetta et al. reported retrospectively on risk factors for mortality in elderly trauma victims. These included high ISS, Glasgow Coma Scale score, and fluid requirement.[25] At the lower extreme of age, there are differences in volume assessment, administration routes, and physiologic responses.[1,26] The need to avoid secondary brain injury in head-injured trauma patients is well understood;[27] however, Dickinson et al. are among those who have highlighted the paucity of information from randomized studies in this area.[28] It is generally thought that hypotension adds to the permanent deficit after brain or spinal injury and that the case for hypotensive strategies here is yet to be established.

The human data allow only broad interpretations to be drawn. Energetic fluid delivery appears to be harmful, but it is unclear in the light of currently available information whether intravenous fluid should be withheld completely

until hemostasis is achieved (delayed regimens) or whether low volumes should be infused to subnormotensive endpoints (permissive regimens). The lower limits of permissive hypotension have yet to be established, although levels low enough to require invasive monitoring for their maintenance have obvious clinical disadvantages.

EVIDENCE FROM ANIMAL STUDIES

Early animal studies examined what is now regarded as controlled hemorrhage. Wiggers'[29] famous experiments involved removal of circulating volume via a catheter until a predetermined blood pressure was reached. Withdrawal ceased before resuscitation began. Thus, the Wiggers model was one of controlled hemorrhage. Traverso et al.,[30,31] in their investigation, exsanguinated to a fixed volume rather than pressure. Their work was an early contribution in the so-called crystalloid-colloid debate.

As stated above, these scenarios represent those cases in trauma where hemostasis can be achieved early (e.g., in isolated limb injury where direct pressure or tourniquet may be applied). If the possibility of further bleeding can be eliminated, it is clear that a normotensive state will be achieved more rapidly by vigorous rather than cautious administration of intravenous fluids. In many trauma patients, however, the bleeding source is not known until a relatively late stage or immediate control of hemorrhage (e.g., by direct pressure) is not possible. In many patients, hemostasis is impossible without surgery. Even if some early compensation can be achieved, it may be unclear whether bleeding is continuing internally or whether physiologic hemostatic mechanisms have successfully brought about the cessation of hemorrhage. Thus, in many cases, including perhaps most of the critically injured, the Wiggers-Traverso model is inappropriate for the assessment of the efficacy of fluid regimens.

To more accurately reflect the clinical scenario of life-threatening hemorrhage, models are required that reflect this uncertainty, and many authors have termed this "uncontrolled hemorrhage." Rabinovici et al.[32] showed that outcome after 15% rat tail amputation was greatly affected if a hemostatic tie was applied before resuscitation with hypertonic saline (HTS). If a ligature was used, HTS had a favorable effect on hemodynamics and on survival. If it was not, HTS increased bleeding, adversely affected hemodynamic indices, and reduced survival.

Krausz explored delayed resuscitation strategies. In a rat tail amputation experiment, he studied administration of HTS at varying times after injury. Early intervention (5–15 minutes) worsened bleeding and mortality, whereas late treatment (30 and 60 minutes) was associated with no benefit. In subsequent research, he compared HTS, large-volume normal saline, and hypertonic sodium acetate resuscitation. He found that all were unfavorable when compared with no treatment.

In contrast, Sindlinger et al.,[33] using 75% rat tail amputation, found that normal saline resuscitation increased survival, although bleeding was also increased. Soucy et al.[34,35] identified anesthetic agents as a possible confounding variable in rat tail amputation models, expressing the view that they were responsible for unwanted vasodilatation and therefore increased blood loss. It was also suggested that most rat models produced insufficient hemorrhage to be of relevance to major hemorrhage in human trauma. Capone et al.[36] stated that tail amputation resulted in unpredictable spontaneous hemostasis and reported that the volume of blood loss was extremely variable. Volume of hemorrhage, size of injury and hemostatic potential following it, timing of interventions, infusion pressures and volumes, and time of follow-up are all crucial variables and may affect outcomes greatly and provide potential problems for the rat amputation model.

Craig and Poole[37] used a different rat study design involving transection of the distal ileocolic artery, causing free hemorrhage into the peritoneal cavity. Clotting was adversely affected and bleeding increased in rats given lactated Ringer's and small-volume hetastarch compared with no treatment.

In a series of classical experiments, an aortotomy model in immature swine was used by Bickell and colleagues.[6] Aggressive fluid resuscitation with lactated Ringer's solution was compared with hypertonic saline/dextran and with no treatment. Both crystalloids resulted in unfavorable outcomes compared with withholding treatment. Delayed hypotension was also investigated by Chudnofsky et al.,[38] who divided porcine subjects into early-treatment and delayed-treatment groups.

Permissive strategies have been examined by Capone et al.,[39] again using rats. After a 3-mL/100 g preliminary bleed, a 75% tail amputation was carried out on 40 rats. These were then divided into four sets for the first 90 minutes. A control set and a delayed-treatment set received no treatment during this period. The other sets were resuscitated to 40 mm Hg and 80 mm Hg. After this initial period, all but the controls were resuscitated to 80 mm Hg and a hematocrit of 30 for 60 minutes. The rats were then observed for 3 days. They concluded that the hypotensive resuscitation strategy carried the best long-term survival, believing this to be evidence for permissive hypotension as a resuscitation strategy.

Stern et al.[40] used a standardized porcine aortotomy similar to that of Bickell. In this series of experiments, resuscitation was guided by pulse pressure. Those animals maintained hypotensively were more acidotic, but suffered lower volume losses and lower mortality than those maintained at higher pressures. Similarly, Owens et al.[41] looked at a limitation of fluid guided by cardiac index using the Bickell's aortotomy method. The experiment simulated prehospital resuscitation phases and went on past definitive surgical repair to mimic an authentic trauma transfer scenario. Standard higher volume resuscitation resulted in some temporary oxygen delivery benefits compared with limited resuscitation, but subsequently also in increased peritoneal bleeding and increased crystalloid and blood requirements.

Riddez et al.[42] compared four fluid replacement regimens in dogs after infrarenal aortotomy. Fluid was withheld in a control group, whereas lactated Ringer's solution was given in ratio of 1:1, 2:1, or 3:1 against expected blood loss in three other groups. The highest mortality was seen in the no-fluid and the 4:1 groups, whereas animals in the 1:1 and 2:1 groups had similar mortality rates. Deaths from rebleeding predominated in the high-volume groups, whereas hypovolemia was responsible in the low-volume replacement animals.

Solomonov et al.[43] have attempted to produce a model relevant to blunt trauma by using a controlled splenic laceration in rats to reproduce massive splenic injury. They found that vigorous infusion of normal saline increased bleeding and decreased survival.

A few authors have established experiments for continuous bleeding, for example, Silbergleit et al.[44] In this study, the benefits of hypotensive resuscitation were less clear cut. Cruz et al.[45] have established a model in rats for further investigating uncontrolled retroperitoneal bleeding.

In some ways, the requirement for increasing sophistication in animal models serves to highlight both the difficulty of human studies and the gap between laboratory and real-life scenarios. Even if blunt trauma can be simulated adequately in animal experiments, it is difficult to envision ways in which the complexity of human responses to injury, including nociceptive reactions, can be replicated. The animal data provide impetus for further evaluation of permissive hypotension strategies.

AN ENDPOINT STRATEGY FOR PRACTICE

The best fluid resuscitation strategy in trauma has not yet been definitively established.[4] It would seem unlikely that one protocol would fit the requirements of all trauma victims as some have attempted to do. Equally, the key to success in the early stages of trauma management is, wherever possible, to avoid complications and unnecessary delays before definitive control of hemorrhage. One recently proposed strategy is the use of the presence or absence of a palpable peripheral pulse as a guide to fluid administration.[46]

The presence of a radial pulse in an adult normally implies a blood pressure of approximately 80 to 90 mm Hg.[24] In general, a blood pressure of this order will be sufficient to maintain vital organ perfusion. Thus, by giving fluids in small aliquots, it is possible to titrate fluid administration within what is essentially a permissive hypotension regimen. In the prehospital setting, it has been further suggested that transfer should not be delayed while intravenous cannulation is attempted, unless the patient is trapped. Cannulation may be attempted en route and, if successful, fluid given in boluses in the manner described above. In this way, delayed and permissive hypotensive strategies can be dovetailed into a practical and simple system that has at least some supporting evidence.

This protocol can be adapted if required. In infants, for example, it may be safer to attempt palpation of a brachial pulse. It is also possible that penetrating torso trauma may prove to require lower resuscitation blood pressures than head injury, in which case, the presence of a central pulse (e.g., carotid; approximately 60 mm Hg) may be selected as the endpoint. Given that the brain is a vital end organ, the presence of effective mentation may also be a usable resuscitation endpoint in the absence of significant head injury.

Such ideas require further validation and research before the case for them can be put any more strongly, but methods similar to these are likely to provide the basis for resuscitation strategies in the near future. It would seem that the era of vigorous fluid resuscitation may be drawing to a close. The current British Army trauma protocol that involves the administration of sufficient intravenous fluid to maintain the presence of a radial pulse offers the optimum outcome for injured soldiers with ongoing hemorrhage. This policy has also been recommended to the American Armed Forces Medical Services by the Delegates at the Combat Fluids Conference at the Uniformed Services University of the Health Sciences meeting in July 2001. It remains to be seen whether the military medical services of other countries will follow their lead.

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