Fluid resuscitation in traumatic haemorrhage

R. CUTRESS

Nuffield Department of Surgery, John Radcliffe Hospital, Headington, Oxford, UK

INTRODUCTION

It is ancient knowledge that stopping haemorrhage is beneficial, and that blood is necessary to sustain life. The world's oldest medical record, a Sumerian clay tablet of about 2150 BC, describes the use of bandages and poultices to stem bleeding. In contrast the Greeks, over a thousand years later, believed that illness resulted from an imbalance of one of four humours: blood, phlegm, yellow bile and black bile. If patients were bleeding, physicians might even have bled them further, in order to remove some of the 'excess bad humour', blood.¹

These beliefs and practices, popularized by Galen, persisted for another 2000 years until in 1628 William Harvey published his work on 'the movement of the heart and blood', which he supported by a long series of experiments. He thus finally overthrew Galen's theories and put an end to blood letting. After this breakthrough, treatment for haemorrhage became more like that which is now familiar; battlefield blood transfusions were first performed during the American Civil War, and prehospital infusion with 5% dextrose was first routinely used by the civilian ambulances in Belfast in 1967. Even since these times, however, controversy has abounded with regard to volume resuscitation in trauma.

Trauma is the commonest cause of death in those aged under 35 years, and the 500 000 British hospital admissions after injury result in 13 000 hospital beds being occupied each day. Since 1988, Advanced Trauma Life Support (ATLS) training has been instituted in the UK. This lays down specific guidelines on how trauma is to be managed, and has greatly improved training, but it has not resolved the controversy. As trauma is so common, and a high proportion of those treated for trauma receive fluid resuscitation, it is clearly an important subject that deserves due consideration. This review aims to assess the efficacy and the scientific basis of fluid

resuscitation in modern treatment (as exemplified by ATLS) of traumatic haemorrhage.

Keywords: haemorrhage, hypovolaemia, resuscitation, shock, trauma

HAEMORRHAGIC SHOCK

Haemorrhagic shock is widely understood to be a clinical syndrome caused by inadequate perfusion of nutrient substrates to the tissues due to haemorrhage.² It was not until the 1940s that Wiggers and co-workers separated shock from haemorrhagic hypotension.³ In a series of classical experiments they withdrew set volumes of blood from dogs and then reinfused the withdrawn (heparinized) blood. They showed that if the volume withdrawn was too great, or if the delay before reinfusion was too long, the blood pressure would not then be maintained by reinfusion of the blood, or by subsequent further infusions. They concluded that, as a result of the withdrawal of the blood, an irreversible process was occurring in the dogs, which they termed 'shock'. They also demonstrated that there was a very wide variation between individual dogs in the insult required to produce shock, and that other variables such as trauma increased the susceptibility of the dogs to development of shock. As well as having obvious clinical implications, this finding demonstrated the need to produce an experimental model that produced shock with reasonable reliability. Wiggers and co-workers therefore developed a model they called the 'Western Reserve Method', whereby the dog was bled to a blood pressure of 50 mmHg, which was maintained for 90 min, and then further bled to a pressure of 30 mmHg, maintained for 45 min. This reliably led to a mortality of 82% within 6 h of reinfusion. All the classic experimental work on haemorrhagic shock has used this model, or a modification of it.

Modern initial fluid replacement therapy in trauma is based on concepts developed by Shires

Correspondence:
Dr Ramsey
Cutress,
1 Mill Close
Hemingford Grey,
Cambridgeshire
PE18 9DJ, UK

*et al.*⁴ working on the Wiggers model. They measured total-body red cell mass using ⁵¹Cr-labelled red blood cells, total body plasma volume using ¹³¹I-labelled human serum albumin, and ³⁵S-tagged sodium sulfate to measure total body extracellular fluid. Using the 'Western Reserve Method' they showed that after the return of the shed blood, both the red cell volume and the plasma volume returned to normal; however, there remained a deficit in extracellular fluid volume. They then determined whether or not replacement of this deficit would improve survival, and observed that it did. If 10 mL kg⁻¹ plasma was added with the shed blood, mortality decreased from 80 to 70%, and if lactated Ringer's solution was added with the shed blood, mortality dropped to 30%.

As there was no external source for the loss of extracellular fluid, the question arose as to whether the fluid moved isototically into the cells. To answer this question, Shires *et al.*,⁴ measured the transmembrane potentials of skeletal muscle *in vivo*, using modified microelectrodes, before haemorrhage, whilst 'shock' was occurring, and during resuscitation, in the animal model. They found that the transmembrane potential dropped from -90 to -65 mV during acute profound haemorrhagic shock, and that this was reversed during resuscitation with the shed blood and Ringer's solution. Muscle biopsies were also taken at all three stages and, using the chloride space methods to measure intracellular sodium, potassium, chloride and water, it was shown that the cells swell, gaining sodium, chloride and water whilst losing potassium. These ionic changes are believed to be due to the depletion of adenosine triphosphate (ATP) and hence the loss of activity of transmembrane pumps, in particular the sodium potassium ATPase. This is one of the key pieces of supportive evidence for the initial use of asanguinous resuscitation fluids as opposed to, for example, O-negative blood in the management of traumatic haemorrhage.

THE ATLS ALGORITHM

Over the past 20 years, arguments have raged as to whether crystalloid is better than colloid in early traumatic shock. It is now generally accepted in North America and some centres in the UK that crystalloid is preferable, largely on the basis of the results of a meta-analysis of the 17 major clinical studies dealing with the issue,⁵ and on the experimental work on the animal model outlined

above. Crystalloid also has the advantage of being cheaper than colloid and non-antigenic, and so it has now been advocated for initial resuscitation of trauma both in England⁶ and in the USA.⁷

The meta-analysis is quoted to show a relative difference in mortality rates of 12.3% in favour of crystalloid in trauma patients. Interestingly, this study is also believed to show a 7.8% mortality difference in favour of colloids in patients with non-traumatic haemorrhage. It is postulated that, in the trauma patient, the stress of trauma leads to a greater increase in the permeability of the pulmonary capillary membrane than is caused by such stress in the non-trauma patient. Leakage of colloids into the interstitium will cause an increase in the incidence of Adult Respiratory Distress Syndrome (ARDS) in the trauma patient given colloids, but not in the non-trauma patient whose basement membrane remains less permeable. Unfortunately, however, even on pooling all the trials together in the meta-analysis, the numbers are still small (a total of 826 patients including the non-trauma groups) for a study that uses mortality as the endpoint. This is reflected by the fact that the parameters defining the 95% confidence intervals for both trauma and non-trauma cases include the value zero. Hence, in this study, for both trauma and non-trauma cases there may be no difference in mortality for either crystalloid or colloid, so in neither case can it be stated whether crystalloid or colloid is preferable, although the results suggest an advantage for crystalloid in the trauma case and for colloid in the non-trauma case. Larger trials providing narrower confidence intervals are needed in order to demonstrate whether such an advantage exists.

ATLS doctrine is that crystalloid resuscitation should begin either in hospital or, if necessary, before the patient reaches hospital, as soon as fluid loss is recognized, or is suspected to have occurred. Signs of fluid loss can be minimal. For example, with 15% (750 mL) blood loss slight anxiety occurs, whilst cardiovascular parameters remain almost normal. As the volume of crystalloid given needs to be three times that of the blood loss for adequate replacement (empirical evidence⁷ and the fact that the total extracellular volume is three times the intravascular volume), fluid resuscitation tends to be aggressive.⁸ Two litres of Ringer's lactate are often given immediately through wide-bore cannulae, when bleeding is suspected to have occurred in trauma.

Subsequent treatment according to the ATLS

algorithm depends on the response to the initial infusion (see Fig. 1). A rapid and sustained response (assumed to indicate satisfactory replacement of loss of less than 20% of the blood volume) is defined as a return to and maintenance of normal cardiovascular parameters such as blood pressure, pulse and pulse pressure, a urine output of 50 mL⁻¹ and an improvement in capillary return and 'CNS status'. Patients who respond transiently are assumed to have lost 20–40% of their blood volume or to have ongoing haemorrhage. Infusion of blood is then commenced and the response observed in order to discriminate between the two. Those patients who do not respond to this treatment, or who did not respond at all to the initial 2 L of Ringer's solution are assumed to have ongoing haemorrhage, and thus the ATLS algorithm states that surgical intervention is indicated in order to stop this.

The normal response to blood loss is an increase in heart rate stimulated by a decrease in venous return (preload). This initially maintains the cardiac output. The blood pressure is maintained by arterial vasoconstriction, leading to increased systemic vascular resistance. If too much blood is lost, these means of compensation fail and blood pressure falls precipitously. The heart and brain, initially protected by autoregulation, are no longer adequately perfused and tissue death begins to occur. If blood volume is maintained above a critical point venous return and hence cardiac

output and blood pressure should be adequate.⁹ Expansion of the vascular compartment is not the only consideration, however, as the blood that reaches the tissues must be adequately oxygenated. Experiments on dogs have shown that acute haemodilution *per se*, without volume loss, is only tolerated to levels of 7 g dL⁻¹ before cardiac compensation is overwhelmed.¹⁰ This is why the ATLS algorithm specifies the need for blood after the initial 2 L of Ringer's solution. Blood clearly also contains many other substances, such as clotting factors, that may be of particular benefit after trauma. It appears that, if haemoglobin can be maintained above 10 g dL⁻¹, with packed red cells if necessary, then oxygen delivery will not be compromised.⁹

IS THE ATLS ALGORITHM SCIENTIFICALLY VINDICATED?

The belief has become almost axiomatic that when fluid is lost it should be replaced. This logic is as inescapable as that championed by Galen. We must be extremely clear as to the intended effects of our treatments, follow this up with experimental evidence from appropriate animal models as well as adequate clinical trials, and hence establish beyond doubt that the algorithm used produces optimal results. This is especially important now that audit has started in the UK to ensure that the ATLS algorithm is being followed.¹¹

Fig. 1. The ATLS algorithm for shock.

Significant criticisms have been levelled at the Wiggers model of haemorrhagic shock, namely that, although the model is extremely effective in demonstrating the fluid shifts that accompany shock and subsequent resuscitation, it does 'not reproduce the primary pathophysiological event leading to haemorrhagic shock, namely a vascular injury'. It will therefore 'not demonstrate how various resuscitation regimens affect hemostasis or how alterations in hemostasis affect outcome'.⁸ Blood loss in trauma does not occur in given volumes through a catheter to a set blood pressure for a certain period of time, but occurs through injury to blood vessels. To a degree, the loss sustained depends at least in part on the normal physiological mechanisms of stopping haemorrhage. This should not be ignored, and unfortunately the Wiggers model does not take this into account. Once blood has been withdrawn via the catheter, further bleeding will not occur through the catheter site on resuscitation.

As long ago as World War I it was recognized that 'the injection of a fluid that will increase blood pressure has dangers in itself. Haemorrhage may not have occurred to a marked degree because the blood pressure has been too low to overcome the obstacle offered by a clot'.¹² The article goes on to describe how resuscitation should only occur with the surgeon present to stop any bleeding. During World War II, the American Surgeon General advocated this advice for treating patients with bleeding that was not readily accessible to external control.¹³

The physiological control of arterial haemorrhage was studied in a series of experiments by Shaftan *et al.*¹⁴ They cannulated the carotid artery and jugular veins of dogs in order to measure blood pressure and give fluid infusions, respectively. They then dissected out the saphenous artery and severed it. They found that haemostasis did not occur in dogs whose blood pressure was maintained at normal levels. This was performed either by transfusion with autologous blood and then saline, or by vasopressors. On the other hand, those animals that were used as a control and were given no fluid produced a 'soft extraluminal clot' that contained the bleeding. This clot was blown away and rebleeding started from the site if the control animals were transfused within the first hour in order to raise the blood pressure back to normal.

Further provocative experiments using a different animal model were performed by Dronen

et al.^{8,15} They deliberately chose a model with a high 1-h mortality where they argued no one would question the need for aggressive fluid resuscitation. They bled pigs through a femoral artery catheter to a mean arterial pressure (MAP) of 30 mmHg. They then produced a 4-mm aortic laceration by pulling a steel wire that they had already sewn in place. When the pulse pressure dropped to 5 mmHg they proceeded to resuscitate with saline at a rate of 6 mL kg⁻¹ min⁻¹ up to a total of 90 mL kg⁻¹ when resuscitation was continued with shed blood at a rate of 2 mL kg⁻¹ min⁻¹. A control group received no resuscitation, and experimental groups were resuscitated to MAPs of 40, 60 and 80 mmHg. They measured 1-h survival and total haemorrhage volumes, amongst other parameters. The 1-h survival value for the control group was 12.5%, while 1-h survival values for the 40, 60 and 80 mmHg groups were 89, 78 and 22%, respectively. Volumes of shed blood were also greater in pigs who were resuscitated to higher MAPs. The conclusion drawn from these results is that, although moderate fluid infusion to maintain lower than normal blood pressures resulted in improved survival, more aggressive resuscitation to normal blood pressures led to decreased survival and increased haemorrhage volumes. In the words of the authors, 'current standard therapy for the treatment of haemorrhagic shock includes initial aggressive colloid resuscitation. Our data suggest that this is not desirable in the presence of a noncompressible vascular injury'.

The concept of keeping blood pressure down in order to reduce bleeding is not unique or restricted to trauma patients. In leaking aortic aneurysms, systolic blood pressure is often maintained between 50 and 70 mmHg using only small volumes of blood or crystalloid infusion. Using this treatment it has been found that cardiac and other vital functions can be adequately maintained whilst keeping blood loss from the aneurysm low.¹⁶ In a recent article¹⁷, a similar approach has been supported in which life-threatening cardiac or major vascular injury is excluded before the infusion of 2 L of clear fluid.

In another experiment using the same swine model, Dronen *et al.* compared resuscitation with saline alone, with resuscitation using saline followed by blood, and with resuscitation using blood followed by saline.¹⁸ The mortality was found to be 100, 37.5 and 25%, respectively. These results, derived from a more appropriate experimental model than the 'Western Reserve Method' of

Wiggers (as used by Shaftan *et al.*), challenge the experimental basis of the use of crystalloid infusion as initial therapy for haemorrhagic shock. It must be noted, however, that although O-negative blood can theoretically be made available as fast as crystalloid, crossmatched blood obviously cannot. A clinical study is needed in order to assess and compare the efficacy of O-negative blood as initial therapy with that of other fluids; this has not been undertaken in a prospective study to date.¹⁹

Although the swine model of Dronen *et al.* is more appropriate in cases of ongoing haemorrhage than that of Wiggers, some criticisms still remain. In the initial two experiments up to 90 mL kg⁻¹ was infused. Weight for weight this corresponds to 7–8 L in a subject weighing 80 kg. ATLS uses only 2 L of crystalloid before blood. In the animals resuscitated to higher blood pressures, a much greater amount of haemodilution would therefore occur than during an ATLS resuscitation, where blood would be added earlier. Secondly, by design these studies assess short-term survival and do not consider renal, cerebral or other end organ damage or survival. Thirdly, in all these cases immediate surgery would be indicated on the basis of non-response to initial saline infusion, if the ATLS algorithm was used. Despite the above criticisms these papers are very useful and, by using a more appropriate model, they clearly reinforce the well-known fact that the definitive treatment of major haemorrhage is haemostasis and not transfusion, and that if ongoing haemorrhage is suspected, cautious fluid administration should be used, avoiding rapid changes in blood pressure. This is especially important now that modern techniques enable us to infuse fluids through peripheral intravenous lines at rates exceeding 800 mL min⁻¹.²⁰

‘SCOOP AND RUN’ OR ‘STAY AND PLAY’

Even before the first ATLS course in 1977, which advocated the earliest possible fluid resuscitation,⁷ there was considerable debate over the benefit of prehospital fluid resuscitation.¹⁹ There has been no evidence to date suggesting that prehospital administration of intravenous fluids is of benefit to trauma patients,²¹ although ATLS as a package has been shown to be more effective in prehospital treatment than Basic Life Support.^{22,23} As described earlier, experience gained during the two world wars has suggested that resuscitation should not begin until the surgeon is ready to stop the

bleeding. Experiments such as those described above have added fuel to the debate. The arguments against the ATLS algorithm include not only the theoretical possibility of blowing off a clot, but also the argument that time spent on on-scene resuscitation was wasted when patients really required the definitive treatment provided by surgery. This argument was strongly supported by a retrospective series of 52 American trauma patients.²⁴ It was found in that study that the mean time taken to establish intravenous access was 11.3 min, and on average only 489 mL were infused, whilst the average time for transport to hospital was 10.7 min. In this case one can strongly question the value of prehospital resuscitation and argue for the ‘scoop and run’ policy. The case must be different in more rural areas, however, where transport times to hospital might be much longer. Physiological computer modelling suggests that prehospital volume resuscitation cannot be useful unless prehospital time exceeds 30 min.²⁵

Kaweski *et al.* in 1990 reported a retrospective study of 6855 trauma patients which suggested that, even when there was no delay caused by the prehospital administration of fluid, this administration did not improve the outcome.²⁶ They divided the patients into three groups depending on initial blood pressure at the scene, and injury severity score, and they found that 56% of the patients had been given intravenous fluids. When the patients who had been given fluids were compared with those, within the same group of injury severity, who had not been given fluids, there was no statistically significant difference in the outcome. The best predictor of outcome was, not surprisingly, found to be the severity of initial injuries. In this series the average transport time to hospital was 37 min, irrespective of whether fluids were given or not. The authors do not state, however, whether those patients who were not given fluids had had an intravenous line placed which, for example, did not work, as in the light of the previous paper, if this were the case in a significant proportion of cases, and if time was wasted inserting intravenous lines that did not work, then perhaps the results could still be interpreted as supporting a ‘scoop and run policy’. In any case this series showed that no advantage was to be gained by fluid resuscitation.

Owing to the results of the previous paper it became more ethically justifiable to perform a prospective trial. The preliminary results (from the first 300 patients) of such a trial have been reported

by Bickell *et al.*²⁷ Patients included in the trial were all those who had gunshot or stab wounds to the trunk. They were randomized according to the calendar day of injury such that those injured on an even day of the month received immediate fluid resuscitation, and those injured on an odd day did not receive any fluid until induction of anaesthesia. As the teams worked one 24-h shift every 72 h, the 24-h periods of immediate or delayed resuscitation correlated with the shifts, and teams alternated between the two groups. In this study there was found to be no significant difference in the rate of survival to hospital discharge, between the immediate resuscitation group (56%) and the delayed resuscitation group (69%). The full results of this unique trial, which may go against the grain of modern teaching on fluid resuscitation, are eagerly awaited.

'ALL BLEEDING STOPS, EVENTUALLY'

If the experiments of Shaftan and Dronen are reproducible clinically such that bleeding is more likely to stop without resuscitation, and resuscitation can be shown to have no positive effect, then one must ask what are the dangers in hypotension or non-resuscitation. Understandably, the greatest concern of anyone dealing with such patients must be that bleeding will stop because the patient has died through inadequate resuscitation. It is intuitive and has become almost axiomatic that if someone is losing volume they should be given volume. This is what makes the above study so unique and so important. The danger, however, is that this study may be interpreted to mean that resuscitation is not indicated in all situations. The results of this study on trunk-penetrating injuries cannot be correlated with other common types of injury, e.g. burns or crush injuries where considerable fluid loss may occur in the absence of severe bleeding, or necessarily with road traffic accidents, which are a major source of trauma. The selection criteria for this study were such that ongoing haemorrhage, poorly responsive to external control, was likely to occur. This type of trauma, where surgery is always ultimately required, is that most likely to benefit from delayed resuscitation.

In Bickell's study it must also be noted that the group of patients who received no fluid prior to induction of anaesthesia received on average about one 1 L on induction. This highlights an

important point. During hypovolaemia blood pressure is maintained to a limited extent by the cardiovascular responses of vasoconstriction and tachycardia. On induction of general anaesthesia these reflexes are lost,²⁸ and the danger is that blood pressure may plummet. This is one of the major risks of not resuscitating until induction of anaesthesia, and the report provides no information about the anaesthetic experiences during the study. Another effect that might be expected if the blood pressure is allowed to stay low would be an increase in the incidence of end organ failure. This does not appear to have been a problem in the study, but it does highlight the point that what is of critical importance is not blood pressure but tissue perfusion, and if bleeding is allowed to stop through hypotension, then a direct index for measurement of tissue perfusion may be needed. Possible indices might be arterial lactate, end tidal carbon dioxide or conjunctival oxygen, all of which have been found to show a degree of correlation with the level of tissue perfusion.^{9,29} These parameters clearly require further study, and at present are probably only useful as an adjunct. Urine production has always been an extremely useful index of renal perfusion, but the obvious problem with this is the time delay before the urine is produced and a reading is obtained. Doppler and oscillometric techniques of measuring blood flow tend to produce errors of a clinically significant magnitude when used in clinical practice. Perhaps if Bickell's study, when completed, clearly shows a requirement for hypotensive resuscitation in the type of trauma patient being studied, then greater emphasis will be placed on finding other more direct means of monitoring the tissue perfusion of the patient. This will enable the blood pressure to be dropped, ensuring minimal blood loss but still allowing confidence that the vital organs are being adequately perfused.

Other differences between Dronen's swine model and that of the trauma patient must be considered, such as the variable spectrum of injuries, degree of tissue damage and nociceptive effect, the variable delay before treatment can begin, and the incomplete knowledge of the emergency clinician with regard to exactly what has occurred. This may be most clearly evident in the ATLS protocol in patients who respond transiently to 2 L of Ringer's solution. These patients may have stopped bleeding, but have lost more fluid than has been replaced, in which case the treatment is to give them more fluid and return their blood pressure to

normal, maximizing tissue perfusion. On the other hand, they may still be bleeding, in which case, as discussed above, the experiments of Dronen suggest that a balance must be struck, selecting a blood pressure at which bleeding is minimized but the vital organs are adequately perfused. What is clearly needed is a means of determining very rapidly which of those two categories a 'transient responder' belongs. At present there does not appear to be any index that indicates whether a patient is actively bleeding. Until that time, it is fair to say that the ATLS algorithm, probably correctly, errs on the 'safe' side.

CONCLUSIONS

There is no doubt that as a package, ATLS provides extremely useful guidelines, and it has been shown to make a substantial contribution to the management of trauma. One of the positive features of the controversy regarding fluid resuscitation that it has shown is that, although ATLS has been of enormous benefit, to improve it, each of its parts must be taken and studied selectively, and be shown to be experimentally and clinically validated.

In conclusion, four key points arise. First, as the model used to support the initial use of crystalloid in haemorrhagic shock is not appropriate in the case of ongoing haemorrhage, and as the meta-analysis of crystalloid against colloid is only suggestive but not significant, a large prospective trial is needed to compare mortality with initial fluid resuscitation using O-negative blood, Ringer's lactate solution, and a colloid. Secondly, whilst two of the studies described show no statistical advantage gained from fluid resuscitation, due to their limitations, and other advantages gained from ATLS as a whole, it is still safer to resuscitate as described in the ATLS protocol, following conventional wisdom, but ensuring that this does not cause any delay in transport and definitive treatment. Thirdly, even if Bickell's study when completed shows that there is an advantage in not resuscitating those with the type of trauma studied, an alternative direct means of measuring tissue perfusion, and a means of establishing whether a patient is actively bleeding, will be needed in order to allow the use of non-resuscitation with fluid, as an option prior to surgery, in some cases. Fourthly, the estimated transit time to hospital will always play an important part in the decision made on how to resuscitate.

One of the fascinating things about medicine is that there can be no rules, but guidelines are clearly needed, and these must be shown to be appropriate. ATLS is appropriate at the moment, but if we are not to fall into the same traps as those who followed Galen for 2000 years we must continue to put it to the test and not accept conventional wisdom unconditionally.

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