Impact of crystalloids and colloids on coagulation cascade during trauma resuscitation-a literature review

Jakub Kaczynski^{1*}, Maria Wilczynska², Joanna Hilton¹ and Louis Fligelstone¹

*Correspondence: jakub.kaczynski@hotmail.co.uk

¹ABM University Health Board, Regional Trauma Centre, General and Vascular Surgery Departments, Morriston Hospital, Swansea, SA6 6NL, UK.

²Hywel Dda Health Board, General Medicine Department, Prince Phillip Hospital, Llanelli, SA14 8QF, UK.

Abstract

Background: During resuscitation trauma patients receive various intravenous fluids, which can exacerbate coagulopathy and haemorrhage further. This led to the introduction of the damage control resuscitation, which advocates minimal intravenous fluids use. However, some fluid may be required in uncontrolled haemorrhage or when blood products are not immediately available. Furthermore, questions regarding the type and volume of the administered fluids remain still unanswered.

Methods: Review of literature.

Results: Crystalloids such as 0.9% Isotonic Saline and Lactate Ringers can cause either a hypercoagulable (lower dilutions) or hypocoagulable (higher dilutions) derangements. Hypertonic Saline (7.5%) leads to more pronounced coagulation abnormalities when compared with 0.9% Isotonic Saline. The effects of the 7.5% Hypertonic Saline combined with 6 % Dextran 70 are controversial. Some authors reported significant clotting abnormalities, but others found an improvement in the haemodynamic parameters. The evidence on human albumin solution use in trauma is very limited and suggests a procoagulant effect at lower dilutions. Gelofusine even with smaller volumes leads to pronounced coagulation abnormalities. All Dextrans (40 and 70) cause significant hypocoagulability at lower dilutions. Similarly lower molecular starches demonstrate a definite hypocoagulable effect.

Conclusions: A literature review has also indicated that none of the studies demonstrated survival or outcome benefit associated with a particular type and volume of administered intravenous fluids. The results are controversial and further research is needed to clarify this issue.

Keywords: Albumins, coagulopathy, dextran, gelofusine, hypertonic saline, 0.9% isotonic saline, lactate ringers, 6% voluven

Introduction

The acute coagulopathy of trauma (ACT) is associated with significant mortality and increases the risk of haemorrhage further [1,2]. It can be caused by the loss of coagulation factors due to haemorrhage, hypothermia, acidosis, trauma and dilution from the intravenous fluids (IVF) administration [3-5]. The circulatory system can be viewed as an electrical circuit ($P = F \times R$) in which P represents pressure difference between the two ends of the vessel, F is blood flow and R is called the vascular resistance [6]. This Ohm's law explains why aggressive resuscitation with IVF may inadvertently lead to more blood loss. This is due to an increase of pressure in the damaged blood vessels resulting in the disruption of the formed blood clot [7,8]. Despite this simple logic, the past management of trauma patients for many years was based on the belief that the use of large volumes of intravenous crystalloids is essential to restore the circulating volume and to achieve the best outcomes [9]. However, several studies found this to be harmful, because it exacerbates the lethal triad (acidosis, coagulopathy and hypothermia) and shock induced inflammatory response [10-12]. This subsequently leads to profound systemic and cellular complications, which cause adult respiratory distress syndrome (ARDS), multi organ dysfunction syndrome (MODS)

and death [12,13].

Fluid resuscitation strategies have evolved substantially over the past decade leading to the introduction of the Damage Control Resuscitation (DCR) model. DCR aims to salvage the trauma patient from disturbed physiology by breaking the lethal triad [14]. DCR utilises three key concepts: permissive hypotension, rapid correction of the coagulopathy and early use of blood products as primary resuscitation fluids (instead of IVF) [8,11]. This appears to be logical giving the fact that all fluids including crystalloids and colloids have the ability to worsen the shock and coagulopathy [15]. One might even argue that we should stop using crystalloids and colloids all together. However, this would be neither a safe nor a practical option, mainly, because some fluid is needed to maintain the systolic blood pressure (80-90 mmHg or palpable radial pulse) in order to continue perfusion of the vital organs (heart and brain) at the expense of worsening peripheral perfusion. This is particularly true when faced with uncontrolled bleeding, for example, during the pre-hospital phase and when blood is not available. This approach has been augmented by the research, which showed that small boluses of crystalloids (250 mls) administered in a controlled manner are beneficial during an active haemorrhage [16]. On the other hand, the fundamental

questions regarding the volume and type of the fluids infused remain still unanswered. Even an updated Advanced Trauma Life Support (ATLS) manual finds it difficult to estimate the amount of intravenous fluids needed during resuscitation [9]. The most logical approach to administration of intravenous fluids appears to be based on patients' haemodynamic parameters and response to resuscitation [16]. Nevertheless, there is enough evidence that the administration of IVF during trauma can have detrimental effects on coagulation cascade. Hence, the knowledge of the IVF induced coagulopathy has an important clinical relevance. This article summarises the current evidence on coagulation cascade derangement caused by various crystalloids and colloids.

Effect of intravenous fluids on coagulation

In general available fluids are divided into two groups: crystalloids and colloids [7]. The crystalloids include isotonic, hypertonic solutions and combination of hypertonic solutions with Dextran. The colloids are subdivided into natural (albumin) and synthetic (Dextran, Gelatine and Starch).

Crystalloids: 0.9% Isotonic Saline and Lactate Ringers

Crystalloids have been the main resuscitation fluids for more than 70 years [17,18]. They became popular during the Vietnam War, when blood became unavailable. Initially their use was thought to be associated with better survival [13]. However, their use soon became associated with the "shocked lung", which later on was defined as ARDS [18]. Numerous *in vitro* studies proved that 0.9% Isotonic Saline (IS) at lower dilutions (10%) acts as procoagulant, but has an anticoagulant effect at higher dilutions [19,20]. Roche *et al.*, replicated the above findings by demonstrating an increased r-time (reaction time, which corresponds to an early clot formation) and reduced α -angle (indicator of the rate of solid clot formation) in thromboelastography (TEG) at higher dilutions (40-60%), which are consistent with the hypocoagulable state. Coats *et al.*, proposed a purely dilutional effect of IS as a primary explanation for this coagulation derangement. However, other authors link it with the impairment of thrombin formation and fibrin polymerisation by the administered large crystalloid volume [21,22]. The hypercoagulability could be explained by the presence of an imbalance between decreased antithrombin III (ATIII) activity and thrombin generation [23]. The IS induced haemodilution, which also results in Platelets (PLT) aggregation, leads to thrombin generation, which subsequently binds with an ATIII [23]. Consequently, consumption of ATIII results in the development of hypercoagulability.

Similarly, Lactate Ringers (LR) demonstrated a hypercoagulable effect at 20% dilution, but hypocoagulable properties with prolonged r-time and reduced α -angle at dilutions >40% [24,25]. In spite of these similarities with IS, several differences and controversies surround these two crystalloids.

The pH of 0.9% IS is only 5 and along with the high sodium and chloride load is responsible for the development of

the hyperchloraemic metabolic acidosis [11]. Surprisingly, despite the presence of the two isomers of Lactate Acid (D and L), LR with the pH of 6.5 is more alkalising solution than IS [10,18]. The isomer L is a naturally occurring one, so can be easily metabolised by the body [24]. In contrast, D-isomer, which cannot be metabolised, is associated with neutrophils activation and subsequently leads to the development of systemic inflammatory response syndrome (SIRS) [11,17,26]. LR cannot be used for infusion with red blood cells, because it leads to the clotting of the blood filters due to calcium citrate content [11]. Also, the presence of potassium can worsen hyperkalemia [26]. All of the above would seem to favour IS, but conflicting results from various studies make it almost impossible to draw the definite conclusions. Some studies advise LR as the primary resuscitation crystalloid, having fewer reported complications with its use in trauma [10,13,17]. Interestingly, no association was found between LR and the degree of acidosis [26]. However, a Cochrane review demonstrated no obvious advantage of one of these crystalloids over the other [27].

Hypertonic Saline (HTS)

In the 1980s Hypertonic Saline (HTS) was introduced as a small volume alternative to the large volume of crystalloids used during the resuscitation [10,28]. Although this fluid is available in several concentrations (3%, 3.5%, 5% and 7.5%), the majority of the available data is based on the 7.5% HTS solution. Animal models of uncontrolled haemorrhage (grade V liver injury) showed that 3% HTS is able to maintain mean arterial pressure at higher levels than LR [29]. 3% HTS was also associated with reduced lung and intestinal complications [29]. DuBose *et al.*, reported reduced mortality after 5% HTS in patients with Glasgow comma scale (GCS) <8, but this did not seem to translate to improvement in neurological function 6 months post traumatic brain injury [30].

The benefits of 7.5% HTS were reported to be superior to lower HTS concentrations [29]. 7.5% HTS is associated with the reduction of intracranial pressure in head injuries and fewer complications, such as ARDS or sepsis [11,31,32]. It has the potential of increasing blood pressure with lower volumes (250 ml) due to rapid shifts of the fluid between the cellular and interstitial spaces [29,31,33]. On the other hand, it carries a risk of the cellular dehydration due to high sodium load and central pontine myelinosis [30,31]. More importantly, the coagulation derangement is much more pronounced when compared with IS. The increase in the r-time and reduced α -angle are noted even at the low 10% dilution [33].

Hypertonic saline with dextran (HSD)

7.5% Hypertonic Saline combined with 6 % Dextran 70 (HSD) was thought to be another compelling option. Unfortunately, many studies delivered conflicting results. Mattox *et al.*, found that HSD is safe, and associated with a lower incidence of coagulopathy. In contrast, Coats *et al.*, revealed the HSD

procoagulant effect at 10% with subsequent rapid increase in deranged clotting at 15% dilution [34]. Rotstein *et al.*, suggested that a small bolus of HSD can be beneficial in haemorrhagic shock, but other research group found that it is associated with a risk of inducing splanchnic ischaemia [13]. Similarly to HTS, the evidence shows that HSD can improve haemodynamic parameters and reduce intracranial pressure [35]. Unfortunately, so far none of the studies demonstrated survival or outcome benefit associated with the use of HTS or HSD and further research is needed to clarify this issue [13,16,35,36].

Natural colloids

Human Albumin Solution (4.5% and 20%)

The evidence on human albumin solution (HAS) use is limited, and results are controversial [37]. No data are available on the 20% HAS and its effect on coagulation cascade. The 4.5% HAS has similar procoagulant effect as IS at 10% dilution [38]. However, Vogt *et al.*, revealed minimal coagulation derangement. Roche *et al.*, found prolonged r-time and reduced MA (maximum amplitude representing strength of the clot) values at 40% dilution with 4.5% HAS. He also showed significantly reduced calcium levels, which can worsen the coagulopathy further. HAS is not routinely used in trauma (except burns) due to the high price, risk of disease transmission and their association with an increased mortality in patients with traumatic brain injury [10,39,40].

Synthetic colloids

The synthetic (non-protein) colloids are classified into gelatines, dextran solutions and hydroxyethyl starches. The current evidence from meta-analyses showed an increased risk of death in trauma patients resuscitated with colloids [16,22]. However, a Cochrane review suggested no differences between crystalloids and colloids [27].

Gelofusine

Uniform results from multiple *in vitro* studies confirm profound anticoagulant effects of Gelofusine with 40% and 60% dilution, which is similar to the one found in patients receiving heparin during haemodialysis [19,21,39,41,42]. *In vivo*, Gelofusine demonstrated greater dilution when compared to IS and overall smaller volume leads to more pronounced coagulation derangement [41,42]. In addition, Gelofusine can cause anaphylactic reactions due to its bovine collagen component [41]. This is believed to be caused by an intrinsic effect of Gelofusine owing to its negative charge [19]. The negative Gelofusine charge interferes with negatively charged phospholipids on PLT by covering the PLT membrane with the colloid's macromolecule [42]. This reduces adhesion and aggregation of PLT resulting in the derangement of the coagulation [42]. However, other authors imply that Gelofusine might influence the weight and reticular network of fibrin strands, due to incorporation of gelatine molecules into the

developing clot [22].

Dextran 40 and 70

The available Dextran solutions are 40 and 70 (Molecular Weight-MW) [39]. Only a few studies in the literature have examined the effect of Dextran 40 and 70 on coagulation profile. All studies report an increased coagulation at 20% dilution with hypocoagulability above 40% dilution with prolongation of the r-time and reduction in MA with Dextran 70 [34,38]. Petroianu *et al.*, reported profound hypocoagulable states at 50% dilution with Dextran 40.

6% Voluven

There are many generations of starches, including 200/0.5, 250/0.5, 450/0.7 and the most frequently used 130/0.4 (6% Voluven) [23,39]. The particular generation is described by the MW and the degree of molar substitution [39,43]. For example, 6% Voluven has a MW of 130 and a molar substitution of 0.4. Trumble *et al.*, suggested that a higher MW leads to a more significant coagulation derangement. However, others proposed that lower molar substitution, allowing for increased starch elimination, minimises the harmful effect on coagulation [22,44].

It remains debatable whether the benefit comes from the lower MW or lower molar substitution. Nevertheless, lower MW starches have shown fewer negative effects such as renal failure and coagulopathy [39]. A hypocoagulable effect of 6% Voluven was revealed *in vitro* at 40 % and 50% dilution by prolongation in r-time and reduced α -angle and MA value [24,38]. Recent studies despite their poor design and lack of statistical significance showed that 6% Voluven reduced mortality with no evidence of coagulopathy in trauma [45-47]. James *et al.*, found that 6% Voluven is associated with better lactate clearance and with no evidence of renal failure. However, this was not the case in the blunt trauma group who in general sustained more severe injuries and were more coagulopathic. It is therefore, unclear whether the presence of ACT in this group of patients prevented them from having any benefit from the 6% Voluven [48]. The significant hypocoagulable effect of the starch could be explained by the blockade of the fibrinogen receptor (GIIb-IIIa) by macromolecules of 6% Voluven [22]. Therefore, as a consequence impaired PLT function with reduced von Willebrand's factor level impairs fibrin polymerisation leading to coagulopathy.

Conclusions

Haemorrhaging polytrauma victims represent the most vulnerable group of patients. Their survival depends on prompt haemorrhage recognition and appropriate resuscitation. An extensive literature review revealed that both crystalloids and colloids can alter coagulation cascade by dilution and intrinsic effects [10,17,19-21,23,24,26,29-31,33,34,38-42, 44-58]. The exact mechanisms by which intravenous fluids

cause coagulation impairment are still poorly understood. Furthermore, the idea of an “ideal” intravenous fluid which would offer oxygen carrying capacity, volume replacement and minimal haemostasis derangement remains elusive. Nevertheless, some fluid replacement therapy may be required when a multiple injured patient suffers from an uncontrolled haemorrhage [16,59]. Although, some evidence supports the use of small volume (250mls) IVF administration in uncontrolled haemorrhage, the results of many studies are controversial and should be interpreted with caution. Crystalloids and colloids are used on daily basis in many surgical and medical specialties. Therefore, knowledge of and the effect of commonly administered fluids on the coagulation process have an important clinical relevance beyond trauma. Future research is required to further clarify this issue.

List of Abbreviations

ACT: Acute coagulopathy of trauma
ARDS: Adult respiratory distress syndrome
ATIII: Antithrombin III
ATLS: Advanced Trauma Life Support
DCR: Damage Control Resuscitation
GCS: Glasgow comma scale
HAS: Human albumin solution
HSD: Hypertonic Saline with Dextran
HTS: Hypertonic Saline
IS: 0.9% Isotonic Saline
IVF: Intravenous fluids
LR: Lactate Ringers
MA: Maximum amplitude
MODS: Multi organ dysfunction syndrome
MW: Molecular Weight
PLT: Platelets
SIRS: Systemic inflammatory response syndrome
TEG: Thromboelastography

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Corresponding author's statement: There won't be any further changes in the authorship, which includes either addition or removal of author's detail. The corresponding author is solely responsible person for all the communications and proceedings that are needed to be done with the publisher on behalf of all authors. JK and MW carried out the literature search, critical appraisal of the evidence and drafted the manuscript. JH and LF carried out the critical revision of the manuscript and helped to re-draft it. Final manuscript was read and approved by all authors.

Publication history

Received: 07-Mar-2013 Accepted: 29-Mar-2013
Published: 02-Apr-2013

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Citation:

Kaczynski J, Wilczynska M, Hilton J and Fligelstone L: **Impact of crystalloids and colloids on coagulation cascade during trauma resuscitation-a literature review.** *Emergency Medicine and Health Care* 2013, **1**:1.
http://dx.doi.org/10.7243/2052-6229-1-1