A PROACTIVE APPROACH TO THE COAGULOPATHY OF TRAUMA: THE RATIONALE AND GUIDELINES FOR TREATMENT

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Introduction

An emerging concept in combat casualty care is that of haemostatic resuscitation: the rapid and proactive treatment of the coagulopathy associated with major injury.

This article reviews the evidence behind this approach and demonstrates how this is used pragmatically in contemporary combat casualty care practice.

Prevalence of coagulopathy in trauma

According to the British Committee for Standards in Haematology and the American College of Pathologists, prolongation of the activated partial thromboplastin time (APTT) and prothrombin time (PT) to 1.5 times the mean normal value indicates a coagulopathy requiring blood product replacement [1-3]. A number of studies have indicated that coagulopathy is common after severe trauma and that it results from a number of causes including metabolic acidosis, hypothermia, dilution of coagulation factors by resuscitation fluids and consumption of coagulation factors [4-10]. Coagulopathy is especially associated with some forms of injury, e.g. brain injury, because of the release of tissue thromboplastins from damaged brain matter [11; 12].

A UK civilian study by Brohi et al [13], using the definitions given above, clearly demonstrated that major trauma patients (Injury Severity Score, ISS >15) can present at hospital with a coagulopathy: 24% of 1088 trauma patients (median ISS 20) analyzed on arrival at the Emergency Department (ED) were coagulopathic. The majority (75%) of patients had suffered blunt trauma and the median time from injury to hospital was 73 minutes; this is compared to 7.6% blunt force (motor vehicle crash, fall, assault, crush) in 876 patients on the UK military Joint Theatre Trauma Registry (01 April 2006 to 30 September 2007, OP HERRICK and OP TELIC only), and a median injury to ED handover time of 97 minutes for UK military priority 1 casualties [14]. The incidence of coagulopathy increased with severity of injury (assessed by ISS), independent of the volume of pre-hospital resuscitation fluid (reliably recorded by a physician). The authors comment that the patients had received minimal pre-hospital fluid resuscitation (median values of 500 ml crystalloid or 1000 ml colloid) and that the development of coagulopathy in these patients was unrelated to the volume or type of intravenous fluid given.

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A second survey [15] based on 8724 severely injured patients (96% blunt injuries) from the German Trauma Registry Database confirms the presence of coagulopathy in 34% of all severely injured patients arriving in the Emergency Department. This study used a similar definition of coagulopathy to that employed by Brohi et al [13] and identified a similar time to hospital. The presence of coagulopathy was positively associated with the volume of pre-hospital fluid, injury severity and delay between injury and arrival at hospital [15]. Even in patients with minimal pre-hospital resuscitation, coagulopathy was present in 10% of cases [15]. Despite the limited statistical analysis in this study it supports the conclusion that coagulopathy is present in a significant proportion of severely-injured patients by the time they arrive at hospital.

Early coagulopathy was also reported by MacLeod et al [16] in a retrospective analysis of 7638 trauma patients admitted to a Level 1 Trauma Centre between Jan 1995 and Dec 2000, although as a group these patients were less severely injured (median ISS 9) than those described by Brohi et al [13]. Additionally, MacLeod et al [16] were unable to account for medication that might have contributed to the coagulopathy, for example warfarin treatment or pre-hospital fluid administration. A number of other smaller studies [17; 18] and anecdotal comments [19]] have also documented coagulopathy in trauma patients on arrival at hospital. Furthermore, early coagulopathy is associated with increased morbidity and mortality [13; 15; 16; 18].

Although it is always a concern that studies with negative conclusions are less likely to be published than those with a positive conclusion, the collective evidence strongly suggests that a proportion of severely injured patients are already coagulopathic by the time they arrive in the Emergency Department and the remainder are at high risk of rapidly developing a coagulopathy. Clearly the true incidence of coagulopathy will depend on the definition adopted. There is evidence that bleeding time and thromboelastographic measurements are better indicators of dilutional and hypothermia induced coagulopathy [20]. Using this methodology the true incidence of coagulopathy associated with major trauma may well be significantly higher than reported.

Proactive treatment of coagulopathy in severely injured casualties

The coagulopathy seen early in trauma patients is multi-factorial and includes hypothermia, acidosis, severity of injury and prolonged hypotension [21; 22]. However, it has been shown that coagulopathy can occur very early after injury where these mechanisms are not necessarily present. Novel mechanisms associated with tissue hypoperfusion [23] and mediated through activation of protein C causing

anticoagulation and hyperfibrinolysis have been postulated [24]. Strategies are already in place in UK military practice to address some aspects of trauma-related coagulopathy: hypothermia is actively managed and has become an uncommon finding [19]. There is also active research at Dstl Porton Down to develop improved military pre-hospital resuscitation strategies to minimise acidosis, which is also aggressively managed early in the hospital phase using agents such as THAM (Trometamol; Tris-Hydroxymethyl Aminomethane) and fluid loading [19].

The early coagulopathy in severely injured casualties is due in part to a reduced concentration of clotting elements in the blood because of consumption and/or dilution [17; 19; 25-27]. The problem is exacerbated as fluid resuscitation continues with fluids that contain little or no functional clotting elements (factors, substrate and platelets) and the use of plasma-poor packed red blood cells (PRBC) will contribute to the dilution of the patient's clotting factors [25]. Resuscitation strategies relating to use of plasma during resuscitation were formulated when whole blood was used for resuscitation, and have not taken account of more recent development such as the use of plasma poor PRBC[25].

During surgery, the loss (and replacement with plasma poor red cells) of 1.4 times the blood volume results in fibrinogen levels falling below critical values for haemostasis and losses of 2.0-2.3 times the blood volume results in deficiencies in prothrombin, Factors V and VII and platelets [28]. The role of FFP and Cryoprecipitate in resuscitation is to replace a range of clotting factors in the recipient's blood and limit the dilution of these factors during resuscitation.

Since a coagulopathy is already present in a significant proportion of trauma casualties or can develop rapidly during resuscitation, and coagulopathy significantly influences outcome, then timely treatment is essential. Unfortunately, current laboratory tests cannot provide the rapid turnaround of results for timely intervention and issue of blood products [18; 29; 30]. The situation regarding point of care assessment of coagulation may improve with the adoption of alternative testing methods such as thromboelastography [18], but the method still requires validation in combat trauma and widespread acceptance. There is, therefore, a current need for proactive treatment. The practice that has been adopted in the US military is the administration of FFP:PRBC (1:1) very early in the in-hospital resuscitation phase [19]. This has also been adopted in UK military practice [31]. In order to facilitate this approach the UK has introduced a transfusion triage process for early identification of casualties likely to require massive transfusion so that an aggressive approach can be adopted.

Evidence supporting the effectiveness of early administration of FFP:PRBC (1:1) to attenuate coagulopathy after trauma

Although the concept of early in-hospital resuscitation with FFP:PRBC (1:1) is based on sound physiological/ haematological principles, there is currently very little objective evidence to demonstrate its clinical efficacy. A retrospective study of clinical practice by Cinat et al [32] has been quoted by some authors as supporting the FFP:PRBC concept. However, Cinat's study [32] identified improvements in patient outcome associated with alterations in clinical practice that included not only more aggressive use of FFP: blood (ratio of 1:1.8 in survivors vs. 1:2.5 in non survivors), but also other haematological changes such as increased use of platelets in addition to correction of hypothermia and alterations in surgical practice. While this study [32] shows a clear improvement in patient outcome over a 10 year period with alterations in clinical management, the study design and analysis does not allow an assessment of which individual or combination of individual changes in practice improved survival. These findings are reinforced by a very recent retrospective analysis [33] comparing two cohorts (before and after a change in policy) which shows that early, proactive, treatment with platelets in addition to FFP:PRBC (1:1 ratio) reduced haemorrhage volume and transfusion requirement while improving coagulation status and 30 day survival in patients suffering massive bleeding after rupture of abdominal aortic aneurysms.

There are, however, publications that specifically address the issue of early resuscitation with FFP:PRBC (1:1), but the majority of these are based on a review of the literature, expert opinion and case series (Grade V evidence based on a modified Delphi method [34]) as well as one study based on non-randomised historical controls (Grade IV evidence).

Grade IV evidence

A retrospective analysis of 246 patients contained in the US Military Joint Theatre Trauma Registry (JTTR) who had received massive transfusion in a Combat Support Hospital over a 22 month period (Nov 2003- Sept 2005) was conducted by Borgman et al [35]. The data shows that non survivors (compared to survivors) had higher injury severity scores, were in a worse physiological state on admission to hospital (lower haemoglobin levels and increased base deficit) and received less FFP and more PRBC (low FFP:PRBC ratio).

Analysis shows an apparently impressive reduction in mortality with shift in balance in FFP in relation to PRBC (mortality of 65%, 34% and 19%, respectively, with low, medium and high FFP: PRBC ratios[1] of 1:8, 1:2.5 and 1:1.14 [35]). Each of these groups is reported as having similar overall injury severities, although severe AIS scores (4-5) for thoracic and head/neck injuries were more common in the low FFP:PRBC ratio group. Differences in mortality remained significant when patients with thoracic injury were removed from the analysis and when those with neurotrauma were separately removed. Unfortunately there is no report of the effects of simultaneously removing severe head/neck and thoracic injuries to balance types of injury between treatment groups. It is also impossible to determine the consequence of combination of factors such as physiological compromise and injury severity and other differences in treatment on outcome.

A further limitation relates to the use of ISS to score injury severity. This scoring system has significant limitations since it does not take into account multiple injuries to the same body region. However, multiple injuries are likely to be of clinical significance since they will impose an additional pathophysiological burden on the patient, which in turn will modify resuscitation requirements and the consumption of coagulation factors by increasing the volume of damaged tissue. The underestimation of injury severity in some casualties will, therefore, limit the power of the analysis. Whilst no summary scoring system will be perfect, the use of the more recent NISS (New Injury Severity Score) may reduce the problem since this does take into account multiple injuries to the same body region.

Despite these limitations, and those inherent in a retrospective study conducted over a period when other aspects of treatment may have evolved, this is an important study that represents the first systematic assessment of the early and aggressive replacement of coagulation factors on survival in the context of military medicine. Studies such as this one are conducted under difficult circumstances and serve as a stimulus for further investigation of this important element of treatment.

[1]FFP:PRBC median ratios (range): Low 1:8 (0:22 to 1:4); medium 1:2.5 (1:3.9 to 1:2.1); high 1:1.14 (1:2 to 1:0.6).

Grade V evidence

The remaining evidence (Table 1) supporting the efficacy of early resuscitation with FFP:PRBC (1:1) is based on anecdotal reports, case series, uncontrolled studies, computer simulations and expert opinion.

Report	Nature of evidence	Recommendation
Ho et al 2005 [25]	Literature review/ expert opinion	Early administration of FFP:PRBC 1:1
Ho et al 2005 [36]	Computer model	Early administration of FFP:PRBC: • 1:1 to avoid coagulopathy • 1.5:1 to treat coagulopathy
Hirshberg et al 2003 [37]	Computer model	Early administration of FFP:PRBC, overall ratio 2:3
Ketchum et al 2006 [38]	Review of clinical practice/expert opinion	FFP:PRBC 2:3 or 1:1
Malone et al 2006 [26]	Review of clinical practice/expert opinion	FFP:PRBC:Platelets 1:1:1
Gonzalez et al 2007 [17]	Retrospective review of trauma patients/ expert opinion (the aim of the study was to assess whether their massive transfusion protocol adequately prevented or corrected coagulopathy rather than specifically assessing FFP:PRBC 1:1)	Concluded that their massive transfusion protocol was currently not adequate to treat coagulopathy and noted that they were now starting to use FFP:PRBC 1:1
Mahoney (unpublished)	Anecdotal report of case series	FFP:PRBC noted as being effective in the majority of cases
Hodgetts (unpublished)	Anecdotal experience from R2E OP HERRICK 5 & 6	FFP:PRBC noted as being effective

Table 1: Summary of Grade V evidence relating to the use of FFP:PRBC

Ho et al [25] presented a comprehensive review of the use of blood and blood products in resuscitation and concluded that the amount of FFP used in early resuscitation should be increased to a ratio of 1:1 with PRBC. They also noted that to date (2005) there had been no prospective trials of this approach. The same group also used a computer model to take a pharmacokinetic approach [36] to compare different FFP transfusion strategies both for the prevention and correction of dilutional coagulopathy. They concluded that a FFP:PRBC ratio of 1:1 was needed to avoid a dilutional coagulopathy, while a ratio of 1.5:1 was needed to correct a coagulopathy [36]. Another computer based simulation [37] concluded that early administration of FFP with the first unit of PRBC was needed to avoid a dilutional coagulopathy and recommended an optimal FFP:PRBC ratio of 2:3.

Ketchum et al [38] conducted a review of clinical practice and concluded that "early administration of plasma as a 2:3 or 1:1 ratio with units of PRBC is advisable in the most seriously injured and massively bleeding individuals".

Malone et al [26] went further in their survey of massive transfusion protocols worldwide and suggested early use of FFP:PRBC:Platelets in a ratio of 1:1:1 during resuscitation of those requiring massive transfusion, although again their conclusion is based on expert opinion and consensus rather than clinical data.

A retrospective analysis of 97 severely injured patients receiving massive transfusion and admitted over a 51 month period (ending in January 2003) concluded that when FFP administration was delayed until after the sixth unit of PRBC, coagulopathy was inadequately treated [17]. The study concluded that coagulopathy is a problem seen in patients on admission to the Emergency Department and that the treatment protocols hitherto employed in their Emergency Department and Intensive Care unit did not correct the coagulopathy for *"reasons [that] are unclear from the data obtained, but may include the inability to correct coagulopathy during ongoing resuscitation with crystalloid fluid and PRBC, or that assessment by the bedside clinician is to accept moderate coagulopathy as an alternative to continuous aggressive blood product administration"* [17].

Gonzales et al [17] describe the initiation of a revised protocol that includes the early administration of FFP:PRBC (1:1) in an attempt to address the problem.

Finally there is anecdotal evidence provided by a British army anaesthetist (author PFM, unpublished) who served on attachment to the 10th Combat Support Hospital (CSH) in Iraq (June-September 2006) where approximately 10% of casualties received by the 10th CSH had very severe injuries and coagulopathy on arrival. There had been a recent change in resuscitation strategy and the following is summarised from his internal reports:

"The change in practice is that packed red cells and the fresh thawed plasma were being given in a 1:1 ratio and plasma was given very early in the resuscitation.

This was combined with point of care testing and active management of acidosis and electrolyte disorders. The effect of this approach was rapid correction of coagulopathy and disordered physiology in the majority of these severely injured patients. The patients who responded were being admitted to the ICU with normal physiology.

Less severely injured casualties could be managed with more traditional resuscitation protocols."

The evidence indicating that patients with major trauma become coagulopathic very early in their clinical progression, and the limited evidence of the effectiveness of early administration of FFP as well as PRBC, was used to develop the emerging clinical strategy of proactive and aggressive use of FFP and PRBC in critically injured casualties presenting to the field hospital in Camp Bastion in Afghanistan from March 2007 (personal experience, authors TJH and PFM).

There is, therefore, a body of evidence (Grade V) to support the early administration of FFP:PRBC during resuscitation of the severely injured and that this strategy can be effective in limiting a developing coagulopathy. However, stronger evidence from controlled trials and experimental studies has not been published to date, although current published opinion suggests that a ratio of 1:1 FFP:PRBC is the most effective. Further work is needed to define the precise ratio.

A step further: use of fibrinogen and other coagulation factor concentrates

Some authors argue that we should consider going a step beyond replacing clotting factors using FFP by administering clotting factor concentrates to reverse the coagulopathy of trauma. The rationale underlying this viewpoint is that fibrinogen deficiency develops earlier than deficiency of any other clotting factor during resuscitation with PRBC [28; 39;

40] and the (physiological) concentrations of clotting factors in FFP are relatively low, hence the volume expanding effect of FFP counterbalances the intended increase in in vivo clotting factor concentration [41; 42]. Consequently the use of clotting factor concentrate may be the way forward, especially if sufficient amounts of FFP are not available within a reasonable time [43]. Fries et al have published a series of studies conducted on anaesthetised pigs to examine the potential utility of fibrinogen and other clotting factors concentrates in a model of traumatic injury and blood loss. In an initial study Fries et al demonstrated that fibrinogen (250 $mg.kg^{-1}$), compared to placebo, normalised the propagation phase of blood clotting after massive (65%) haemodilution with a gelatin solution and significantly reduced blood loss from a Grade III [44] liver injury (12 cm long, 3 cm deep cut in the right liver lobe). In a further study [45] the same group compared the effects of placebo (saline) with a combination of fibrinogen (200 mg.kg-1) concentrate and prothrombin complex concentrate (PCC, 35 IU.kg-1) on blood loss and 120 minute survival in anaesthetised pigs subjected to dilution of the plasma with hydroxyethyl starch solution (to induce a dilutional coagulopathy) followed by Grade III liver injury. The group of animals given fibrinogen/PCC had significantly larger numbers surviving to 120 min and reduced blood loss after the liver injury compared to those treated with placebo. In addition, the coagulopathy was reversed and there was no evidence of thromboembolic complications based on gross pathology or histology [45]. It is, however, important to note that both gelatin and hydroxyethyl starch solutions may specifically interfere with fibrinogen as part of their mechanisms of coagulopathy [46-49], thus possibly resulting in a bias in favour of a positive effect of fibrinogen in studies where haemodilution or resuscitation has been achieved with these colloids.

A number of experts in the field suggest that the use of fibrinogen may be the next major advance in the treatment of the acquired coagulopathy associated with trauma[2], and that the use of fibrinogen may allow compensation for thrombocytopenia in the injured casualty [50]. Interesting parallels have been drawn from the obstetric literature where it is reported that women with normally higher plasma fibrinogen levels (approximately 4 g.l-1) suffer less blood loss during childbirth than women with lower (≤ 2 g.l-1) plasma fibrinogen [51]. Although it is also important to note that current guidelines indicate that PCC should only be used in cases of proven factor deficiencies, this is clearly an area of potential development.

Finally, since haemostasis is in part dependent on an appropriate balance between fibrinogenesis and fibrinolysis, and recent studies have suggested that early coagulopathy associated with trauma may include an element of hyperfibrinolysis [24] it would seem appropriate to use antifibrinolytic drugs in the treatment of early coagulopathy. Although antifibrinolytic drugs, such as aprotinin and tranexamic acid, are viewed as valuable pharmacological adjuncts to control surgical bleeding [52], the evidence in trauma is embryonic. Some animal studies, using models of incompressible bleeding, have shown a reduction in haemorrhage volume and increased short term survival after treatment with antifibrinolytic agents [53] while others have shown no such benefit [54; 55]. Consequently, it is too early to determine whether antifibrinolytic drugs will have a role in controlling traumatic bleeding, but the results of an ongoing clinical trial (CRASH2 [56]) may provide an answer.

[2]U Martinowitz, B Sorensen, comments made in presentations at a meeting entitled "Bleeding, clotting and haemorrhage – an update" organised by The Association of Anaesthetists of Great Britain and Ireland, London 04/12/07

Conclusions

There is clear evidence that a significant proportion of severely injured casualties are coagulopathic on admission to hospital and that there is a need to proactively treat the condition. Taken collectively, the evidence currently supports the recommendations for the early use of FFP:PRBC (1:1) during the resuscitation of severely injured casualties. The evidence is predominantly Grade V so that the recommendation itself is Grade E on a modified Delphi scale [34]. The most relevant supporting evidence needs to be derived from observations on human casualties and it is claimed that sufficient data will soon be available to assess the full benefits of damage control resuscitation in the relevant population of critically injured casualties [19]. It is unrealistic to expect a prospective randomised clinical trial in this circumstance and specific questions may need to be addressed in animal models. In addition, the situation regarding resuscitation is currently very fluid. The UK has already introduced a system to transport platelets to operational theatres that to date has been 100% successful i.e. every shipment has been satisfactory. Systems, based on those adopted in civilian practice [57], could also be used to limit potential waste of unused blood deployed far-forward with MERT teams. The active discussion of these other aspects of treating coagulopathy (e.g. fibrinogen, platelet and rFVIIa administration and the use of fresh whole blood [19; 26; 29; 30; 38; 43; 45; 58]) must be taken into account when planning any future trials.

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