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Acute Blood Loss during Burn and Soft Tissue Excisions: An Observational Study of Blood Product Resuscitation Practices and Focused Review

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Abstract

Background—Many military and civilian centers have shifted to a Damage Control Resuscitation (DCR) approach, focused on providing oxygen-carrying capacity while simultaneously mitigating coagulopathy with a balanced ratio of platelets and plasma to red blood cells. It is unclear to what degree this strategy is used during burn or soft tissue excision. Here we characterized blood product transfusion during burn and soft tissue surgery, and reviewed the published literature regarding intraoperative coagulation changes. We hypothesized that blood product resuscitation during burn and soft tissue excision is not hemostatic and would be insufficient to address hemorrhage-induced coagulopathy.

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This study was conducted under a protocol reviewed and approved by the US Army Medical Research and Materiel Command Institutional Review Board and in accordance with the approved protocol.

The authors have no conflicts of interest to report.

AUTHOR CONTRIBUTIONS

HFP designed the research, performed experiments, analyzed and interpreted data, and wrote the manuscript. CLI assisted with analyzing and interpreting review data, and with writing the manuscript. MCH, CGF, and BSS performed experiments, and assisted with analyzing and interpreting data, and editing the manuscript. CE White, SEW, CE Wade assisted with interpreting review data, and with editing the manuscript. KKC assisted with interpreting data and editing the manuscript. APC designed the research, and assisted with interpreting data and editing the manuscript.

Methods—Consented adult patients were enrolled into an IRB-approved prospective observational study. Number, component type, volume, and age of the blood products transfused were recorded during burn excision/grafting or soft tissue debridement. Component bags (pRBCs, FFP, PLTs, and cryoprecipitate) were collected and the remaining sample harvested from the bag and tubing. Aliquots of 1/1000th the original volume of each blood product were obtained and combined, producing an amalgam sample containing the same ratio of product transfused. Platelet count, rotational thromboelastometry, and impedance aggregometry were measured. Significance was set at $p < 0.05$.

Results—Amalgamated transfusate samples produced abnormally weak clots ($p = 0.001$) particularly if they did not contain platelets. Clot strength (48.8 ± 2.6 mm; reference range: 49–71 mm) for platelet-containing amalgams was below the lower limit of the reference range despite PLT:RBC ratios greater than 1:1. Platelet aggregation was abnormally low; transfused platelets were functionally inferior to native platelets.

Conclusion—Our study and focused review demonstrate that further work is needed in order to fully understand the needs of patients undergoing tissue excision. The three studies reviewed and the results of our observational work suggest that coagulopathy and thrombocytopenia may contribute to intraoperative hemorrhage. Blood product resuscitation during burn and soft tissue excision is not hemostatic.

Keywords

Damage control resuscitation; Burn Excision; Soft tissue excision; Acute traumatic coagulopathy; Severe hemorrhage

INTRODUCTION

Severe, non-compressible hemorrhage is the main cause of potentially preventable death in both military and civilian trauma patients (1–5); however, unlike compressible hemorrhage, efforts to develop treatments for this widely recognized problem have yet to yield effective solutions. In both the civilian and military settings, most deaths due to hemorrhage occur in the prehospital environment (1, 4). Performing trauma research protocols in the prehospital setting, in addition to being logistically difficult, is a heavily regulated process that often entails community consent, could potentially pose risk to the patient due to demands on emergency care providers, and requires significant human and institutional resources (6–9). While prehospital research is possible in rural community and smaller community settings, resources are more likely to be found at major urban trauma centers where transport times are short, often 15 minutes or less (8–10). In contrast, military casualties requiring transfusion reach definitive care approximately 50 minutes after injury (11), increasing the risk of irreversible hemorrhagic shock. Transport times can be even longer for civilians living in rural communities and for armed forces operating in remote locations (12, 13).

Given the degree of mortality associated with this clinical problem and the difficulties of studying prehospital hemorrhage, characterizing the effects of significant intraoperative bleeding on coagulation may be an alternative source of data to guide the treatment of acute blood loss in other settings. Such a study could further lead to therapies aimed at mitigating

hemorrhage with potential application for prehospital patients, although caution is warranted. Prehospital and surgical hemorrhage differ in important ways, but studying early changes in coagulation due to significant intraoperative blood loss could offer clues regarding processes that eventually progress to acute traumatic coagulopathy in prehospital trauma patients. Burn and other soft tissue surgical excisions, like trauma, result in tissue injury and hemorrhage, and offer practical advantages. Consent is possible because these surgeries are typically scheduled a day or more in advance. Support staff is available to obtain blood samples, complex analytical instruments can be used, and the onset and time-to-control of bleeding can be accurately determined. Conversely, unlike trauma in the prehospital setting, tissue injury is already present prior to initiation of acute bleeding during excisions. Other important differences include the administration of vasoactive medications and the timing of resuscitation, both of which occur concurrently with blood loss.

Regardless of the applicability of this research to other clinical settings, studying effects of hemorrhage during burn and soft tissue excision on coagulation would provide data regarding an under-studied entity. To date there are only three small studies in this patient population. None of these attempted to characterize the nature and quality of blood product resuscitation during surgery, a necessary first step to understanding intraoperative changes in coagulation. Recent practices in many military and civilian centers have shifted to a Damage Control Resuscitation (DCR) approach which is focused on providing oxygen-carrying capacity while simultaneously mitigating coagulopathy with a balanced ratio of platelets and plasma to red blood cells (14, 15); however, it is unclear to what degree this strategy is used during burn or soft tissue excision. Operative procedures to address burns and soft tissue injury result in considerable bleeding (16, 17). Intraoperative blood loss is estimated at approximately 9.2% of blood volume for every 1% of total body surface area (TBSA) burn excised (18). Furthermore, burn surgeons anecdotally report progressive development of microvascular bleeding, evidence that a coagulopathy may be evolving. The focus of this paper is to characterize the blood products transfused and assess whether they would be adequate to address such a coagulopathy, if present.

While a full characterization of coagulation changes during burn and soft tissue excisions is currently underway at our institution, enrollment in that study is not yet completed. Intraoperative factor deficiencies have been described (19–21); however, reports are out of date because publication preceded important changes in burn care and resuscitation. Here we review the published literature regarding admission and intraoperative coagulation changes after burn, identify important knowledge gaps, and report results regarding the quality of intraoperative resuscitation products and practices from a prospective, observational study. We hypothesized that blood product resuscitation during burn and soft tissue excision is not hemostatic and would be insufficient to address hemorrhage-induced coagulopathy.

METHODS

After obtaining informed consent, patients over the age of 18 who were scheduled for burn excision and grafting or other soft tissue debridement with expected blood transfusion at the US Army Institute of Surgical Research Burn Center were enrolled into an IRB-approved prospective observational study. Number, component type, volume, and age of the blood

products transfused during the case were recorded. Component bags of pRBCs, FFP, PLTs, and cryoprecipitate (CRYO) were collected and the remaining sample harvested from the bag and tubing. Aliquots of 1/1000th the original volume of each blood product were obtained and combined, producing an amalgam sample containing the same ratio of product transfused into the subject. Additional components (excluding CRYO) were purchased and samples analyzed as a quality control measure. Amalgam combinations described above were reproduced, along with additional combinations at a ratio of 1:1:1, to create amalgam samples taken from the bag itself. These were analyzed separately and compared to amalgams from transfused components to assess similarity of results.

Sample analysis

Platelet count (ADVIA ® 120 Hematology System, Siemens Medical Solutions USA, Inc, Malvern, Pennsylvania) was measured. Rotational thromboelastometry (ROTEM®, Tem International GmbH, Munich, Germany) was performed on samples activated with recombinant tissue factor (EXTEM, Tem International GmbH, Munich, Germany). Cytochalasin D (FIBTEM, Tem International GmbH, Munich, Germany) was used to inhibit platelets to differentiate between platelet and fibrinogen (EXTEM) versus solely fibrinogen (FIBTEM) contributions to clot strength. Aprotinin (APTEM, Tem International GmbH, Munich, Germany) was used to inhibit fibrinolysis and compared to EXTEM results to examine effects on measures of lysis at 30 minutes (LI30), 60 minutes (LI60) and at maximum lysis (ML).

Impedance aggregometry (Multiplate® multiple electrode aggregometer, Verum Diagnostica GmbH; Munich, Germany) measured platelet aggregation response to the following physiologically relevant agonists: adenosine diphosphate (ADP), arachidonic acid (ASPI), collagen (COL), ristocetin (RISTO), and a thrombin receptor agonist, thrombin receptor activating peptide or TRAP (ADPtest®, ASPItest®, COLtest®, RISTOtest®, and TRAPtest® reagents, Tem International GmbH, Munich, Germany). As sample volume allowed, aggregometry was also performed on aliquots of individual platelet concentrates. A blood sample was taken from the patient immediately before or during surgery for comparison with amalgam platelet count and TRAP-stimulated impedance aggregometry.

Results were analyzed according to post-hoc determination of the type of blood product transfusion received by the subject: packed red blood cells (pRBC) alone (R-TX); fresh frozen plasma (FFP) with red blood cells (RF-TX); or platelets (PLT), FFP and pRBC together at a ratio of 1:1:1 (RFP-TX). Amalgam samples composed with purchased components (PUR) were similarly labeled R-PUR, RF-PUR, and RFP-PUR, respectively. Box plots were created according to the method described by Tukey. Data was reported as mean ± standard deviation or median [IQR], as indicated by data distribution. Data were analyzed with unpaired Student's T-test, one-way ANOVA or one-way ANOVA on ranks, followed by Bonferroni's or Dunn's tests for multiple comparisons, as appropriate. Significance was set at $p < 0.05$.

RESULTS

Of the 36 subjects enrolled between March, 2013 and July, 2014, 32 received blood products (89%, range: 1–17 units). Specifically, 86% received pRBC, 72% received FFP, and only 17% received PLT. Age of red cell (pRBC), FFP, and PLT components that were transfused during the operation were 25 ± 7 , 362 ± 2 , and 3.4 ± 1.1 days from collection at time of transfusion, respectively. Components purchased to validate amalgam sample integrity were as follows: packed RBCs (n=3) analyzed between days 21–27 of storage, 5-day old thawed plasma (n=3) from FFP, and platelets (n=2) at day 5 of storage. Aliquots and half aliquots of the purchased products were used in different combinations and ratios to create a total of 28 similar amalgam samples, of which 2 were R-PUR, 14 were RF-PUR, and 12 were RFP-PUR. Of the 32 amalgam samples from transfused components, 6 were R-TX, 19 were RF-TX, and 6 were RFP-TX. One subject received FFP alone and was excluded from analysis.

As expected, R-TX and RF-TX amalgam sample platelet counts were significantly lower compared to subject blood samples, whereas RFP-TX amalgam and subject platelet counts did not differ significantly (Figure 1). RFP-PUR platelet counts were higher than RFP-TX, but the differences did not reach statistical significance ($188 [105–281] \nu 135 [140–346] \times 103/\mu\text{L}$, $p=0.268$). EXTEM CT values differed in amalgam samples containing plasma concentrates (RF-TX & RFP-TX, Figure 2A) compared to R-TX, whereas alpha and MCF differed only if platelets were present (RFP-TX, Figure 2B–C). Amalgamated transfusate samples produced abnormally weak clots (Figure 2C; $p=0.001$) particularly if they did not contain platelets. Even when platelets were present, amalgam clot strength (48.8 ± 2.6 mm; reference range (22): 49–71 mm) was below the lower limit of the reference range despite PLT:RBC ratios greater than 1:1.

CT ROTEM results for the amalgams recreated with purchased components were similar compared to those from transfused components ($p=\text{NS}$). Other R-PUR ROTEM parameters were not within detectable limits. RF-PUR and RFP-PUR median alpha angle were somewhat better than those for RF-TX and RFP-TX for alpha angle ($56 [49–75]^\circ$ and $74 [69–76]^\circ$ compared to $45 [33–62]^\circ$ and $68 [62–70]^\circ$, respectively), although differences did not remain statistically significant in post hoc comparisons ($p=\text{NS}$). RFP-TX and RFP-PUR EXTEM MCF differed significantly ($48.8 \pm 2.6 \nu 59.8 \pm 1.5$ mm, $p=0.001$). RFP-TX and RFP-PUR FIBTEM MCF values were similar ($p=11.6 \pm 0.6 \nu 12.7 \pm 1.0$ mm, $p=\text{NS}$), indicating that fibrinogen levels were similar.

TF-initiated clot formation time (CFT) was abnormal for all groups (both TX and PUR samples) and statistical analysis of the data for R and RF groups was not possible, as values were beyond the time limit for the assay in most cases. Values from RFP-TX and RFP-PUR samples, while statistically different, were within reference ranges (22) (145 ± 23 s, $n=6$; 88 ± 7 , $n=12$; $p=0.012$). Maximum lysis (ML), measured as percent loss in clot stability, was very abnormal in some R-TX (range: 3 – 100%; 4 of 6 samples > 10%) and RF-TX (range: 1 – 82%; 5 of 18 samples > 10%) samples, but differences between post-hoc groups were not statistically significant (R-TX: $14.3 [3.3–47.0]$; RF-TX: $3.8 [1.9–17.8]$; RFP-TX: 5.0 ± 3.1]; $p=0.317$). Fibrinolysis was within manufacturer-specified normal ranges in RFP-TX samples (range: 4–10%; 6 of 6 samples > 10%). LI30 and LI60 were similarly within expected

ranges and did not differ between groups ($p = 0.05$). No significant differences were seen between APTEM samples compared to EXTEM ($p = 0.05$). Lysis was not evaluated in the PUR samples.

Platelet aggregation was abnormally low in all platelet-containing amalgam samples regardless of component origin (Table 1), despite a higher percentage of PUR samples with adequate platelet counts. No values were within expected ranges. Even platelet concentrates, which were analyzed without adjusting the platelet count, displayed markedly low aggregation, with largely undetectable responses to ADP and collagen, and only a few results within reference ranges (23) in response to the other agonists (Table 1). Comparison of TRAP-activated RFP-TX and subject impedance aggregation confirmed that transfused platelets were functionally inferior to native platelets (Figure 3), as were the platelets from the purchased components.

FOCUSED REVIEW

Admission Coagulopathy

Multiple studies have demonstrated that severe injury, particularly in the setting of significant hemorrhage, results in coagulopathy in 24–38% of trauma patients (11, 24–27). While definitions for acute trauma-related coagulopathy differ, an international normalized ratio of >1.2 – 1.5 is often used (11, 26–28). The etiology of coagulation deficits is likely multifactorial in the general trauma population, including a well-described coagulopathy associated with high volume crystalloid resuscitation, acidosis, and hemorrhagic shock (26, 29–31). Recently, clinicians have recognized that coagulopathy is present prior to exogenous resuscitation, with likely additive effects contributed by crystalloid and pRBC resuscitation with delayed administration of platelets and plasma. Timing of blood product transfusion appears to be important, in that early resuscitation with balanced products (RBC:plasma:platelets) delivering the approximate functionality of whole blood is associated with better outcome (32), but this has not been fully evaluated in burn patients. A clear association of coagulopathy with increased morbidity and mortality was described in the general trauma population (11, 26–28), but studies in burn patients have not been consistent. One study, in which the criteria used for defining coagulopathy were fairly strict (INR >1.3 , aPTT >1.5 times mean normal, and PLT = 150 – $440 \times 10^9/L$), reported no cases of burn patients with acute coagulopathy of trauma at admission (33), whereas another found that early coagulopathy (INR >1.2) was present in 39% of burned subjects and that it was an independent predictor of mortality by logistic regression analysis (34, 35), a finding in line with other studies (36, 37).

Platelet Dysfunction Due to Trauma

Platelet dysfunction may explain why lower platelet count, a well-described consequence of severe trauma and an independent predictor of mortality, is associated with poor outcome even when within reference ranges (38, 39). While platelet dysfunction is almost certainly a feature in coagulopathy of trauma (40), its role after burns is not clear. Platelet count is typically within reference ranges at admission, then decreases at approximately 3–5 days after injury, particularly if burns are large ($>40\%$ body surface area) (41, 42). Platelet factor

4 (PF4) and TxB2 are elevated after burns, indicating significant platelet activation and consumption in severely burned patients. Studies are lacking that fully evaluate the effect of platelet count on outcome or whether dysfunction is present after burns.

Perioperative Coagulation Status

Three prospective studies to date have examined perioperative coagulation status in burn patients, of which two compared intraoperative values to those from non-injured, elective surgery controls (Table 2) (19–21, 43). These data suggest that burn patients experience a change in coagulation dynamics related to high volume intraoperative blood loss and possibly exacerbated by resuscitation using non-hemostatic fluids. Because preoperative coagulation parameters were high, levels remained above lower reference limits during excision and grafting (E&G) procedures despite significant intraoperative decreases (Table 3) (19–21). The significance of the intraoperative decrease is not well understood; however, because optimal levels of coagulation parameters have not been established. It is possible that values within reference ranges may be inadequate for burn patients, given the elevated baseline levels of factor VIII (FVIII) and fibrinogen in all three studies. Conversely, both the Cullen et al. and Chang et al. papers demonstrated that recovery curves in burn patients return measurements to normal levels that are approximately parallel to non-burn surgery patients (19–21). FV was similar at baseline, but both burned and non-burned subjects experienced a steep decline after surgery, possibly related to high volume blood loss. However, Chang and colleagues showed that after surgery, burn patients experience a faster recovery of factor V (FV) to baseline levels compared to non-burned individuals (20). This suggests that the mechanisms for recovery of FVIII may also be adequate, possibly indicating that, as the authors suggest, burn patients do not need replacement of coagulation factors and platelets intraoperatively.

The study by Niemi and colleagues; however, suggests otherwise. Platelets, coagulation tests, and thromboelastography were abnormal at baseline, and the intraoperative consumptive coagulopathy in burned patients worsened, possibly exacerbated by hemodilution (21). This resulted in deficiencies in several coagulation factors (Table 3), and PT, aPTT, and thromboelastographic measures were consistent with coagulopathy and decreased clot strength during E&G (21). Intraoperative development of coagulopathy in burned patients is further supported by observations from burn surgeons at our institute who note that microvascular bleeding increases progressively during E&G (personal communication).

A limitation of the Chang and Cullen studies is that they do not report the quantity of blood products transfused (19, 20). Conversely, Niemi and colleagues provided detailed information regarding the changes in coagulation status during excision and grafting and blood transfusion during surgery (21). Collectively, these studies indicate that, prior to surgery, burned patients have heightened levels of FVIII and fibrinogen, that FVIII is consumed more rapidly during excision of the burn wound, but that factor levels recover more rapidly (Table 3). Results regarding preoperative platelet levels differed; however. Interestingly, all three papers concluded that precipitous decreases in coagulation parameters and platelet counts (Table 3) are not concerning, despite evidence to the contrary in the

Niemi et al. study (19–21). Given the risks associated with active hemorrhage and blood product replacement, and the well-described hazards of large-volume crystalloid resuscitation, the goal of minimizing blood loss and subsequent transfusions justifies efforts to prevent the development of an intraoperative coagulopathy during E&G procedures.

Most clinicians agree that minimizing blood transfusion is desirable and necessary to decrease infectious and other risks, but the idea of doing so with early hemostatic resuscitation does not enjoy widespread consensus. An alternate strategy is to employ restrictive transfusion strategies during surgery, a philosophy based on the assumption that intraoperative blood loss is inevitable and not substantially altered by concurrent transfusion therapy (44–46). In this setting, hemodynamic instability related to fluid needs could be treated with crystalloid or non-blood colloids. Others suggest that equal ratio transfusion is not necessary during burn or soft tissue excision. While this position is not supported by definitive data, one small prospective randomized trial (n=8 per group) comparing a 1:1 versus 1:4 FFP to RBC ratio failed to find a difference in INR or PT/PTT (47). Additionally, data from the Hébert, et al. study in 1999 (48) comparing restrictive versus liberal transfusion has been frequently generalized to the burn population, and was recently supported by an observational study in burned children with historical controls (45) and a retrospective review (44). Conversely, multivariate analysis did not identify an association between restrictive transfusion and improved survival in a retrospective review by the authors of the latter study covering a similar time span (46).

An alternative method of minimizing intraoperative blood loss may be early resuscitation with balanced blood products, but, as with any resuscitation strategy for burn and soft tissue surgery, this requires further study. The rationale, based on studies in trauma patients with coagulopathy (49, 50), is that early transfusion including coagulation factors and platelets will prevent bleeding by supporting better clot formation (15). The underlying assumption, supported by the limited intraoperative burn data reviewed above, is that bleeding results in coagulopathy during burn surgery. While the study by Palmieri et al. did not demonstrate a difference in INR or PT/aPTT, equal component ratio transfusion did decrease overall pRBC use (47). This approach assumes that transfusing equal ratio blood products to restore whole blood functionality will minimize blood loss. As with the restrictive method, this transfusion strategy has not been fully explored in the surgical treatment of burn and soft tissue injury, thus potential risks and benefits are unclear. A comprehensive study to describe coagulation changes associated with acute hemorrhage during burn and soft tissue excisions is currently underway at our burn center, and may yield important findings to guide future studies.

DISCUSSION

Our data demonstrated that resuscitation during burn surgery is not hemostatic, and platelet dysfunction is present in both burn/tissue injury subjects and in the products used to resuscitate them. Given the results of the Niemi et al. study and those reported here, excisions for burn and soft tissue injury likely result in coagulation deficits and warrant further study. Defining this population in a larger study would potentially resolve some of

the inconsistent findings among the three papers reviewed, and could suggest potential therapies requiring further research.

Our post-hoc analysis of platelet count in our subjects demonstrated that physicians tailored their transfusion strategies to the patient's baseline status. Those with the highest platelet count received fewer transfusion products, whereas those who received all component types had the lowest baseline platelets. The majority of patients received pRBCs and PLTs alone, indicating that, unlike strategies used for many trauma resuscitations, a balanced component approach using equal ratio products is not routinely practiced for active bleeding during tissue excisions.

Rotational thromboelastography results, as expected, generally reflected the composition of the transfused products with a notable exception. While platelet-containing products resulted in the highest clot strength measured, values were still below reference range limits and below comparable TEG measurements from patient samples in the Niemi et al. study. This provides evidence that transfused platelet products do not have the capacity to mitigate the loss of clot strength during acute hemorrhage. Given that the FIBTEM MCF, which isolates the fibrinogen contribution to clot strength, was within reference ranges, the abnormal EXTEM MCF is largely a reflection of a deficit in platelet function. Amalgam platelet counts varied, but were not sufficiently low on average to explain MCF results. Since the ratio of platelets and plasma to RBCs was higher than 1:1:1 in our amalgam samples, this finding indicates platelet functional deficits, which was supported by the platelet aggregation data.

Aggregation data, which was only obtained from platelet-containing samples, demonstrated performance that was below reference ranges for all transfusate amalgams, regardless of agonist used. Surprisingly, even platelet concentrates, which were not diluted prior to testing, displayed very abnormal results, with only 4 concentrates testing within the reference range of one of the agonists used. This lack of responsiveness is likely due to the platelet storage lesion, a well-described consequence of storage over time, particularly at room temperature. Mean platelet age was only 3 days for the transfused components; however, thus well within the storage period of 5 days. Some authors have suggested that stored platelets recover function after transfusion, but data proving this hypothesis are lacking.

The results of the focused review and the data from this study indicate that our understanding of coagulation functional changes during burn and soft tissue excisions are inadequate, that assumptions about the hemostatic function of transfused products are erroneous, and that further study of this matter is warranted and may suggest opportunities for improving patient outcome through improved resuscitation. Obtaining consent for the subjects included in this study was feasible and these patients might have benefitted from interventions to minimize blood loss. While not all the studies reviewed reported coagulation factor results outside of reference ranges, all three documented precipitous decreases in platelet counts and factor levels during surgery (19–21). This was echoed by our own work, in which we found that platelet counts were low in some of the post-hoc groups, similar to findings from the Niemi et al. paper. In combination, these data suggest

that those with abnormal platelet counts may also have coagulation factor deficits and coagulation tests consistent with hemorrhage-related coagulopathy, but this requires further study and a larger patient population than any studied to date. Published data from acutely bleeding trauma patients suggests that platelet dysfunction is a feature of coagulopathy of trauma (40). In the setting of preexisting low platelet counts as seen in the burn and soft tissue injury populations, a similar phenomenon could explain the extent and volume of intraoperative bleeding associated with E&G and other soft tissue excisions. This could also be a fruitful avenue of future research leading to new therapies potentially benefitting severely injured military personnel.

This observational study had some limitations. Because amalgams were created using samples recovered from the bag and tubing, it is possible that sample degradation may have explained some of the results. A second phase of the study using purchased components addressed this question, and, while findings indicated that some parameters were mildly better in the purchased products, most results were similar. Platelet aggregation results from the 'optimally-treated' samples displayed platelet dysfunction that was similar to those from platelet components transfused during surgery (Table 1).

In conclusion, our study and focused review demonstrate that further work is needed, both to define a population that may contribute important findings regarding the effects of acute hemorrhage, and in order to fully understand the needs of patients undergoing tissue excision. The three studies reviewed and the results of our observational work suggest that coagulopathy and thrombocytopenia may contribute to intraoperative hemorrhage. Blood product resuscitation during burn and soft tissue excision is not hemostatic and is insufficient to address such a hemorrhage-induced coagulopathy.

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Figure 1. Comparison of amalgam versus subject platelet count in samples from red cells alone (R-TX); plasma with red cells (RF-TX); or all three components (RFP-TX). Bars show significant differences between amalgam post hoc groups, whereas the symbol § indicates differences between subject and amalgam platelet counts ($p < 0.05$).

B

ALPHA (°)

C

MCF (mm)

Figure 2.

Thromboelastometric analysis of amalgam samples containing packed red blood cells (pRBC) alone (R-TX), fresh frozen plasma (FFP) and pRBC (RF-TX), and platelets (PLT) with FFP and pRBC (RFP-TX). Horizontal lines indicate statistically significant differences. A. Tissue factor-initiated (EXT) clotting time (CT, n = 6 R-TX, 18 RF-TX, and 6 RFP-TX); B. EXT alpha angle (ALPHA, n = 3 R-TX, 15 RF-TX, and 6 RFP-TX); C. EXT maximum clot firmness (MCF, n = 6 R-TX, 18 RF-TX, and 6 RFP-TX); D. RFP-TX MCF comparison with (FIB) and without (EXT) cytochalasin D to inhibit platelets (n = 6).

Figure 3.

Impedance aggregometry with the platelet agonist, thrombin receptor activating peptide (TRAP), performed on amalgam samples containing platelets with FFP and pRBC made from transfused product (RFP-TX, n=5) and purchased components (RFP-PUR, n=12), on subject blood samples (SUBJECT, n=5) collected for comparison, and on platelet concentrates (PLT CONC, n=5). The dashed horizontal line indicates the lower limit of the reference range (23) and the solid horizontal lines indicate no statistically significant difference (NS). Amalgam samples (RFT-TX and RFP-PUR) were significantly lower compared to SUBJECT (*p 0.001) and PLT CONC (§p 0.001).

Table 1

Platelet (PLT) aggregation (Area Under the Curve/10, U) in PLT-containing samples representative of the combined blood product(s) transfused

A. Platelet-containing amalgams contained an aliquot from each blood component transfused (Transfused RFP); packed red blood cells (R), fresh frozen plasma (F), and platelet (P) +/- cryoprecipitate (C). Aliquots were taken from tubing aliquots or residual post-transfusion volume. Amalgam composition is shown in the left column. Platelet components (PLT CONC) were tested independently of the amalgams as sample volume allowed. **B.** As a quality control measure to confirm that the results in A were representative of actual bag content, amalgam combinations in A were reproduced, along with additional combinations, using purchased components (Purchased RFP), excluding cryoprecipitate, to create amalgam samples taken from the bag itself. Additional abbreviations: ASPI = arachidonic acid; COL = collagen; RISTO = ristocetin; TRAP = thrombin receptor activating peptide; NA = Not available due to insufficient sample volume.

Transfused RFP amalgam composition [§]	PLT count (×10 ³)	AGONIST-STIMULATED AGGREGATION (U)				
		ADP	ASPI	COL	RISTO	TRAP
R5F7P1C1	98	0.0	0.0	0.0	3.0	0.0
R10F5P2	135	1.5	0.0	0.0	9.6	10.0
R3F2P1	113	1.3	0.0	0.0	0.8	15.1
R2F1P1	209	0.0	16.6	0.5	6.5	27.7
R1F1P1	352	0.0	27.4	0.0	6.7	41.4
PLT CONC	642	2.2	4.6	1.3	8.6	22.9
PLT CONC	1674	0.0	77.3	4.0	18.3	63.1
PLT CONC	1593	0.0	0.0	0.0	12.9	60.1
PLT CONC	NA	0.0	NA	NA	NA	69.2
PLT CONC	1666	0.2	32.5	11.1	19.6	68.3
PLT CONC	1123	0.0	83.6	7.8	23.0	70.3
Purchased RFP amalgam composition [§]	PLT count (×10 ³)	AGONIST-STIMULATED AGGREGATION (U)				
		ADP	ASPI	COL	RISTO	TRAP
R10F5P2	140	0.0	0.0	0.0	0.0	10.2
R10F5P2	144	0.0	0.0	0.0	0.0	7.6
R1F1P1	456	0.0	0.0	0.0	5.9	44.6
R2F1P1	246	0.0	0.0	0.0	8.9	31.8
R2F2P1	247	0.0	0.0	0.0	9.5	31.6

Purchased RFP amalgam composition [§]	PLT count (×10 ³)	AGONIST-STIMULATED AGGREGATION (U)				
		ADP	ASPI	COL	RISTO	TRAP
R1F1P1	512	0.4	28.9	0.0	3.5	46.1
R2F1P1	379	0.5	21.4	1.5	0.8	32.5
R3F2P1	198	0.0	0.0	0.0	1.0	17.4
R5F7P1	103	0.0	0.0	0.0	0.0	8.6
R5F7P1	116	0.0	0.0	0.0	0.0	3.0
R14F10P3	143	0.0	0.0	0.0	1.0	16.6
R14F10P3	178	0.0	0.0	0.0	0.0	15.6
PLT CONC	1435	1.6	0.0	0.0	32.3	61.5
PLT CONC	1661	0.1	55.1	0.0	52.5	48.6

[§] PLT CONC are apheresis platelets containing the equivalent of 6 units of PLT each, thus platelet:red cell ratios were 1:1 in all samples.

Bold = value reference range (23) (PLT CT: 150–400 × 10³/μL; ADP: 36–101 U; ASPI 42–100 U; COL 24–79 U; RISTO (high dose) 27–124 U; TRAP 75–137 U); TRAP-stimulated aggregation in PLT CONC samples was statistically different compared to RFP and RWB (p<0.001).

Table 2

Comparison of three perioperative coagulation studies in burn patients (19–21).

STUDY	Number of E&G cases studied	Average TBSA Burned (range)	Operation on PBD	Timing of blood draws	Resuscitation	Parameters measured	Key Findings
Cullen, et al. 1989	12 *	46% (20–60%)	7–14	Pre-op (BL) Post-op POH 4, 12 POD 1, 2	pRBCs Ringer's lactate	PT, aPTT, TT PLT CT FIB FV, FVII, FVIII, FIX	1 Burn patients have BL levels of PLT CT, FV, FVIII, FIX, and FIB within or above RR. 2 Levels of PLT, FVIII, and FIB decreased significantly during E&G, but remained within or above RR.
Chang, et al. 1995	23 §	29% (2–59%)	7–14	Pre-bleed (BL) Q 33% calculated TBV resus	pRBCs Ringer's lactate	PLT CT FIB FV, FVIII, FIX	1 Burn patients have BL levels of PLT CT, FV, FVIII, and FIX, FIB in or above RR. 2 Levels of FV, FVIII, and FIB decreased significantly during E&G, but remained within or above RR.
Niemi, et al. 1998	13	35% (13–75%)	2–6	Baseline (BL) Q 4 pRBCs POH 4 POD 1	pRBCs, FFP, PLT (ratio: 2.5 : 1.1 : 1.0) Hydroxyethyl starch Albumin Ringer's acetate	PT, aPTT Hb, Hct PLT CT FII, FV, FVIII, AT III, PLT CT, and FIB changes during E&G were consistent with consumptive coagulopathy possibly exacerbated by hemodilution. FIB, D-dimer (plasma & sera) TEG	1 BL levels of PT%, aPTT, FV, AT III, and PLT CT are below or beyond RR. 2 PT%, FV, FVIII, AT III, PLT CT, and FIB changes during E&G were consistent with consumptive coagulopathy possibly exacerbated by hemodilution. 3 Clot formation rate and strength was low at BL and decreased significantly during E&G.

* 12 surgeries in 9 patients, data compared to published data from 12 non-burned elective surgery patients.

§ Data compared to data from 6 non-burned surgery patients.

Abbreviations: E&G – excision and grafting; TBSA – total body surface area; PBD – post burn day; POH – post operative hour; POD – post operative day; BL – baseline; pRBCs – packed red blood cells; FFP – fresh frozen plasma; PLT – platelets; Q 4 pRBCs – each time 4 units of pRBCs were transfused; Q 33% calculated TBV resus – every time 33% of calculated total body volume was resuscitated with colloids and/or crystalloids; RR – reference ranges; Hb – hemoglobin; Hct – hematocrit; PLT CT – platelet count; PT – prothrombin time; aPTT – activated partial thromboplastin time; TT – thrombin clotting time; FII – Factor II; FV – Factor V; FVII – Factor VII; FVIII – Factor VIII; FIX – Factor IX; FX – Factor X; FIB – fibrinogen; AT III – antithrombin III; TEG – thromboelastogram.

Table 3

Change in intraoperative coagulation parameters during excision and grafting (19–21).

STUDY	PT	aPTT (s)	FV (%)	FVIII (%)	FIX (%)	AT III (%)	PLT CT ($\times 10^3/\mu\text{L}$)	FIB
Cullen, et al. 1989	Baseline	12.4 s	25.3	132	127	–	282	>800 mg/dL
	Intra-op	14.2 s	29.8	> 50	≈ 120	–	> 200	>300 mg/dL
	Post-op	NA	NA	NA	NA	–	NA	NA
Chang, et al. 1995	Baseline	–	–	126	283	128	–	629 mg/dL
	Intra-op	–	–	71	174	99	–	375 mg/dL
	Post-op	–	–	109	220	123	–	461 mg/dL
Niemi, et al. 1998	Baseline	67%	44	>85	≈ 250	–	48	$\approx 6 \text{ g/L}$
	Intra-op	32%	53	≈ 42	< 100	–	59	< 2 g/L
	Post-op	61%	37	≈ 65	≈ 150	–	94	>3 g/L

Abbreviations: PT – prothrombin time; aPTT – activated partial thromboplastin time; FV – Factor V; FVIII – Factor VIII; FIX – Factor IX; AT III – antithrombin III; PLT CT – platelet count; FIB – fibrinogen. Bold values represent values below the minimum limit (PT%, FV, AT III, PLT CT) or prolonged beyond (aPTT) standard reference ranges for healthy subjects.