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Research Article

Serial Changes in Fibrinolysis during and Following Resuscitation of Severe Hemorrhagic Shock in Patients Requiring Immediate Operation

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Introduction

The treatment priorities of the severely injured patient include airway, breathing, and circulation. Establishment of an airway and ventilation typically occur prior to or shortly after arrival in the emergency department. Restoration of circulation involves replenishing body fluid compartments and stopping bleeding in transit to the operating room. The key elements to resuscitation have been established for some time and include packed Red Blood Cell (RBC) replacement of blood loss, fresh frozen plasma (FFP) restoration of procoagulants, and Balanced Electrolyte Solution (BES) to restore plasma volume and to accommodate the obligatory BES relocation into the interstitial fluid space as part of interstitial and cellular homeostasis following severe hemorrhagic shock [1].

FFP restores the procoagulants in both the extrinsic and intrinsic coagulation pathways which lead to the activation of Factor X; this, in turn, leads to the sequential activation of Factor V, Factor II (prothrombin), and Factor I as fibrinogen is converted to fibrin [2]. Under normal circumstances, there is a constant conversion of fibrinogen to fibrin through the action of thrombin, which is balanced with a constant breakdown of fibrin by plasmin in order to maintain a physiologic balance. Thrombin activity is controlled by the coagulation pathways, whereas, plasmin activity is controlled by tissue plasmin activator which, in turn, is balanced by plasminogen activator inhibitor [3]. Previous reports have suggested that the hypotensive insult stimulates an increase in plasmin activity resulting in fibrinolysis, which potentially may compromise the coagulation profile in an actively bleeding patient [4,5]. This concern led to a prospective assessment of serial fibrinogen (FI) levels and both fibrin and Fibrinogen Split Products (FSP) during and after resuscitation from hemorrhagic shock. The hypothesis was that hypofibrinogenemic patients would have increased lysis and, therefore, would be candidates to receive Epsilon-Aminocaproic Acid (EACA), which blocks plasmin activity and, therefore, blocks fibrinolysis [6]. EACS was previously used by the first author (CEL) in hypofibrinogenemic patients with hemorrhage pancreatitis. Surprisingly, this study in injured patients showed that lysis was not present during or shortly after operation for control of active bleeding when the patients were hypofibrinogenemic; since this was a negative result, the data were never submitted for publication. Recently, several publications suggest that an antifibrinolytic agent given to the severely injured patient with hemorrhagic shock will counter the adverse effects of indigenous fibrinolytic activity [7-10]. Despite the plethora of papers recommending this therapy, there have been no measurements of FSP. This manuscript reports these prior measurements of serial FI levels and FSP during and following immediate operation for control of bleeding in patients receiving massive transfusions.

Methods

This study was part of a prospective evaluation of organ function after severe hemorrhagic shock. All studies were approved by the institutional investigational review board and all data were stored in a de-identified research trauma program registry. Consent was properly obtained for each serial study. The criteria for inclusion consisted of a major injury with severe hemorrhage causing the systolic blood pressure to fall below 80 torr and requiring a minimum of six RBC transfusions during immediate operation.[1] If the systolic blood pressure never went below 80 torr, the hemorrhagic insult had to require a minimum of eight RBC transfusions during immediate operation for control of bleeding. The initial 32 patients were treated from July 1977 through June 1979. They sustained gunshot wound in 26 patients, stab wound in five patients, and blunt injury in one patient. The resuscitation policy was to provide RBC transfusions to correct acute anemia, FFP to restore procoagulants sufficient to sustain clotting, and Balanced

Electrolyte Solution (BES) to restore body fluid compartments; none of the patients received supplemental albumin or artificial colloid, which are known to drive procoagulants out of the plasma into the interstitial fluid space [11].

The design of this project was to measure these parameters during operation (study 1), during the first half (study 2), and the second half (study 3) of the subsequent fluid sequestration period which averaged 30 hours, during the first 48 hours (study 4) and the second 48 hours (study 5) of the later mobilization period which averaged 5.1 days, and during outpatient convalescence (study 6) at an average of 22 days. F1 was measured by a fibrometer [12,13]. The amount of F-I in a plasma sample correlates inversely with the clotting time of dilute plasma following the addition of thrombin. The concentration of F-I, in mg/dL, is determined from a previously constructed calibration curve. The plasma F-I level was measured on 150 occasions in 32 patients. The presence of fibrin monomers in the plasma was measured by the addition of protamine sulfate, which dissociates soluble complexes that are formed between fibrin monomers and fibrinogen molecules, particularly fragment X [14-16]. The dissociated fibrin monomers polymerize and form a clot with a positive test being reported when a solid clot or fibrin strands form at any of the subsequent dilutions [14]. Fibrin monomers, primarily fragment X, were measured on 150 occasions in 32 patients. The FSP were measured by the Thrombo-Wellco Test, which involves the addition of a suspension of latex particles, coated with specific antibodies to F-1, to a sample of plasma while observing the mixture for agglutination [14]. The amount of FSP, namely monomers D and E, can be semiquantified by utilizing serial dilutions with the resultant range being 0 to more than 80 mcg/ml. The normal serum level of FSP does not exceed 10 mcg/ml, [14] whereas, significant fibrinolysis is considered to be present when the FSP exceed 40 mcg/ml [14,17]. The FSP were measured on 150 occasions in 32 patients. All samples were collected by a dedicated research associate and prepared for immediate analyses in duplicate to insure accuracy.

From 1979 until 1982, the protamine sulfate test was modified to quantitatively measure fibrin monomers, primarily, fragment X; the normal value is less than 30 mcg/mL. During this interval, measurements of F-I, FSP, and fibrin monomers were made on 73 occasions in 55 patients; these measurements were made during the fluid sequestration period in 28 patients, during the fluid mobilization period in 44 patients, and during convalescence in one patient.

The serial changes in the F-I levels were compared statistically utilizing the unpaired student t test with Bonferroni adjustment. The serial changes in F-I levels were correlated for the total group and the quartiles. The relationship of the F-I level to the presence or absence of fibrin monomers was analyzed by Fisher's exact test comparing patients with an F-I equal to or less than 250 mgm/dL to those patients with an F-I level greater than 250 mgm/dL. The quantified fibrin monomers in the latter portion of the study were correlated with the simultaneously measured F-I levels.

Results

During the initial phase of this study, a total of 32 previously healthy patients met the criteria for inclusion and had measurements of F-I, FSP, and FM during operation.[1] None of the patients had brain injury. The average EMS run time from scene to hospital was five minutes; this data piece was not stored in the research trauma program registry. Upon admission, they had an average ±SD systolic blood pressure and pulse of 76±35 torr and 131±53 beats/minute, respectively. The time from admission to hospital until the patient exited the operating room averaged 7.2±2.8 hours; during this time, they received an average of 18.4±12.3 RBC units, 1199±584 ml FFP, and 15.5±12.3 L BES; the shock time, during which the systolic pressure was less than 80 torr, averaged 54±55 minutes. The intraoperative study time (study 1) averaged 3.9 hours (range 1-8 hours) after admission to hospital.

Six of these 32 patients died. All six presented with no recordable blood pressure or pulse. Five of the six deaths occurred on the operating table, whereas, the last patient died at 40 hours of multiple organ failure. These six deceased patients received an average of 30.1 units RBC, 1250 ml FFP, and 28 L BES during operation, which averaged 4.9 hours. Their intraoperative F-I level was 90.6±11 mg/dL and the FSP averaged 7.5±2.9 mcg/ml; five of these six deaths tested negative for FM, whereas one tested positive.

The 26 patients who survived after being studied during operation received an average of 15.7±2.7 RBC units, 1060±556 ml FFP, and 12.9±5.9 L ES during operation, which lasted an average of 7.6±2.7 hours. Their average F-I during operation (study 1) was 140.5 mg/dL, whereas the average FSP was 7.8±0.4 mcg/ml; none of these 26 patients had a positive test for FM (Table 1). These 26 patients entered into an obligatory postoperative fluid uptake phase which averaged 30.2 hours, during which they received an average of 2.45 units RBC, 148 ml FFP, and 10.3 L BES. Once maximal fluid uptake occurred, as determined by daily weights, vital signs, BES needs, and urine output, they entered into a fluid mobilization period which averaged 5.1 days. During the first four days of the fluid mobilization phase, they received an average of 1.4 RBC units, 22 ml FFP, and 11.3 L BES.

Study #	1 N=26	2 N=26	3 N=26	4 N=26	5 N=26	6 N=14
Study time (hrs)	5.1±2.0	14.4±6.9	26±15.5	47.4±12.4	82.8±15.4	520.0±355.0
Fibrinogen (mg/dL)	140.5±34.2	164.1±36.7	250.2±98.7	456.1±149	578.3±174	503.2±157
FSP* (mcg/ml)	7.7±0.3	13.6±2.8	15±4.7	20±4.5	27±4	18±0.7
Study Temp (°F)	97.2±1.4	983±2.2	98.9±1.6	99.7±1.4	99.6±1.1	98.6±1.0 (N=11)
Study pH	7.32±0.07	7.41±0.07	7.42±0.05	7.46±0.04	7.46±0.05	7.39±0.007 (N=2)
Monomers Negative Positive	 26 0	 25 1	 22 4	 18 8	 15 11	 11 3
*FSP exceeded 40 mcg/dL in one patient during the second and third studies, in two patients during the fourth study, in eight patients during the fifth study, and in three patients during convalescence (study 6).						

Table 1: Demographics During the Serial Studies on 26 Survivors.

The serial measurements of F-I, FSP, arterial pH temperature, and FM were made on four occasions postoperatively in all 26 patients at an average of 14.4, 26, 47.4, and 82.8 hours after admission and following discharge in 14 patients at an average of 520 hours after admission (Table 1). The F-I progressively rose during the five in hospital studies from 140.5 mgm/dL during operation at an average of 5.1 hours (range 1-8) after admission to an average of 578 mgm/dL on intra-hospital study five (Table 1). The F-I levels were significantly greater than the previously measured level during each of the five intra-hospital studies (Table 2). There was also an increase in the number of patients who tested positive for fibrin monomers with the higher levels of F-I. Only three of the 26 patients with F-I levels less than 250 mgm/dL had positive monomers; in contrast, 24 of the 74 patients with F-I levels greater than 250 mgm/dL had positive monomers ($p=<0.01$ by Fisher's exact test). Throughout the six study periods, the F-I level correlated positively and significantly with the FSP by linear and logarithmic correlation coefficient ($p<0.001$ for both, Figure 1). This positive and significant correlation was true for the first quartile of F-I levels less than 166 mg/dL ($p<0.002$), for F-I levels in the inner quartiles from 166 to 495 mg/dL ($p<0.001$), but not for F-I levels in the fourth quartile more than 494 mg/dL ($p=0.71$).

Study No.	1	2	3	4	5	6
Mean±SD (mg/dL)	140.5±34.2	164.12±36.7	250.27±98.7	456.1±149	578.3±174	520.0±355
N	26	26	26	26	26	14
	1	2	3	4	5	6
1 (p Value)		0.0328	0.0001	0.0001	0.0001	0.0001
2			0.0002	0.0001	0.0001	0.0001
3				0.0001	0.0001	0.0001
4					0.0092	0.3565
5						0.1882

Table 2: Serial Fibrinogen Levels Following Treatment for Severe Hemorrhagic Shock. Statistical analysis done by unpaired t-test with Bonferroni correction; each inpatient study (one through five) showed a significant increase in fibrinogen compared to prior study. Using a one-way ANOVA, each study was statistically different ($p<0.001$) from the previous study.

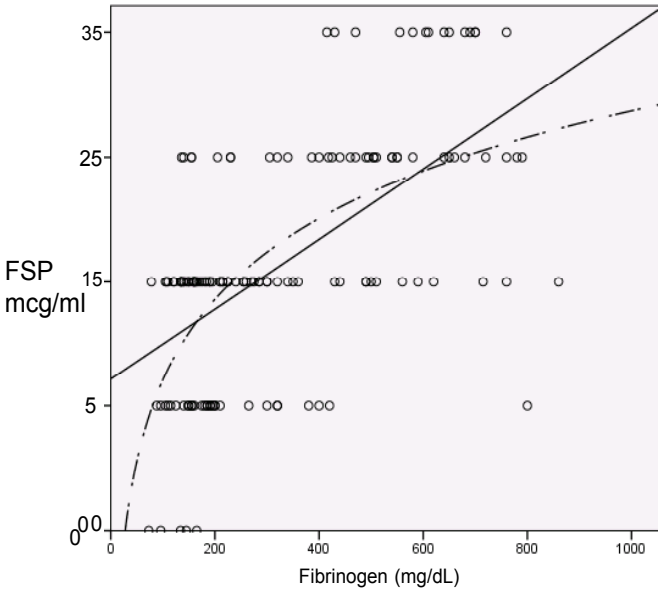

Figure 1: The FSP, throughout the study period, correlated significantly (p=0.001) with the simultaneously measured serum fibrinogen levels. This relationship was also true for the first quartile of fibrinogen levels less than 166 mg/dL (p<0.002), for the inner two quartiles for fibrinogen levels of 166 to 494 mg/dL (p=<0.001), but not for the fourth quartile with fibrinogen levels more than 494 mg/dL (p=0.71).

The measurements of the F-I and the FSP made on 28 occasions during the fluid sequestration period and on the 44 occasions during the later fluid mobilization period correlated closely with the measurements summarized above. The quantitative measurements of FM during this same period correlated significantly (p=<0.04) in a positive manner with the simultaneously measured F-I levels.

Discussion

Ideally, the balance between the fibrin synthesis and subsequent fibrinolysis would serve the patient's well being to maintain control of bleeding and facilitate cellular perfusion. This assumption, however, is controversial. Many years ago, Risberg reported increased fibrinolysis in both man and animals early after injury and attributed this process to the increased release of plasminogen activators by the injured tissue [4]. Starzl and coworkers, utilizing the old and slower technique of Thromboelastography (TEG), confirmed increased fibrinolysis in patients undergoing liver transplantation [5]. More recently, Brohi and coworkers found elevated levels of D-dimer in acutely injured patients; this correlated with increasing injury severity scores and base deficits [18,19]. Recent studies suggest that the balance between fibrin deposition and fibrin breakdown goes awry after injury and that antifibrinolytic treatment might be beneficial [7-10]. The CRASH-2 study reported a prospective randomized double-blind trial with 274 trauma centers in 40 countries involving over 20,000 patients treated within eight hours of injury by tranexamic acid (TXA) as a 1 gm bolus followed by 1 gm given over the next eight hours [8,20]. The TXA treated patients had reduced mortality from all causes (15.5% versus 16.0%) and death from bleeding (4.9% and 5.7%) compared to a placebo control group [8,20]. A follow-up report emphasized that TXA may be detrimental if given more than three hours after injury [7]. A subsequent retrospective study of injured soldiers reported that TXA improved coagulation especially after massive transfusion [7]. The assumption, in these studies, was that the benefits of TXA resulted from the inhibition of plasmin activity but no measurements of FSP or FM were made. It is possible that the beneficial effects of TXA may be related to another effect which has not been identified.

These assumptions, however are controversial. DeBarres and coworkers did not observe fibrinolysis in a hemorrhagic and ischemic swine model associated with a 35% hemorrhagic insult [21,22]. Although the swine became severely coagulopathic, there was no evidence of fibrinolysis as determined by TEG; they did not measure FSP or FM. Valle and coworkers reported that patients who received TXA at an inner-city trauma center were at greater risk of dying when compared to matched historical controls that received no TXA [23]. The TXA-treated patients required more BES, more RBC, and more total fluid in the preoperative and intraoperative periods [23,24]. These authors suggested that TXA might induce hypotension in patients with marginal circulatory volumes; this is a warning on the TXA package insert [24]. They concluded that TXA should be avoided once patients reach a Level I trauma center where immediate RBC, FFP, and BES therapy are given [24]. They did not measure FSP or FM. Starzl, and coauthors, initiated treatment with EACA in patients undergoing liver transplantation only to see that there was an increased mortality rate due to deaths from thromboemboic events [25]. No FSP or FM were measured. Further clouding the issue is he observation that ingested alcohol may impair clot formation in the TEG assay; [2] as many as 30-50% of injured patients arrive at Level I trauma centers with positive serum alcohol levels [26,27].

Clearly, there is a need to define the natural history of F-I physiology during hemorrhage, during intraoperative control of bleeding, and following successful operation. The present study demonstrates that patients presenting to an inner-city Level I trauma center with severe injury do not have increased fibrinolytic activity once resuscitation has been initiated. Absence of significant lysis was seen during operation as early as one hour after admission and during the early postoperative period at an average of 14 hours after admission.

Combined with prior studies, the data, herein, support the presence of a triphasic response of fibrinolysis to hemorrhagic shock. There is increased fibrinolysis during the initial period of hemorrhagic shock, followed by absence of fibrinolysis

after resuscitation is initiated even though the patient is still hyperfibrinogenemic, followed again by increased fibrinolysis which parallels a rebound, or delayed, hyperfibrinogenemia. The teleological rationale for this triphasic response is speculative. The authors propose that this triphasic response is mediated by cytokines. During the preoperative hypotensive period, the cell is subjected to an oxidative insult so that anything which interferes with cellular perfusion such as efficient clotting would be harmful; [28] fibrinogenolysis at this time would impair capillary thrombosis and would be perceived by the cell as sustaining cellular perfusion. Once resuscitation occurs, the cellular receptors sense restored perfusion and shut off the release of fibrinolytic agents which, then, would potentiate recurrent bleeding leading to a recurrent cellular oxidative insult. This late rise in serum fibrinogen after resuscitation from hemorrhagic shock likely reflects increased synthesis and has been demonstrated in both porcine and canine hemorrhagic shock models [29,30]. The progressive rise in F-I and lysis on day two through day four following operative control of hemorrhage is likely related to factors other than coagulation, possibly, related to the reparation of injured cells. This late rise in lysis would also be protective against thrombotic complications [31]. Regardless of mechanism for this triphasic response, these data demonstrate that the restoration of perfusion pressures with intraoperative resuscitation eliminates hyperfibrinolysis and, therefore, obviates the need for any antifibrinolytic agents at this time.

This study has a number of weaknesses. First, F-I consists of three pairs of polypeptide chains with a molecular weight of 340 kDa [12,13]. Thrombin cleaves these fibrinopeptides resulting in a number of breakdown products. Both the cleavage of fibrinogen and fibrin by plasmin yields fragments X, Y, D, and E [13,14,15]. The breakdown products of fibrin and fibrinogen are probably similar and dependent on the polypeptide chains within the total molecular mass [16,17]. The study, herein, looked only at fragment X as being representative of the FSP and at monomers D and E which were only quantified in the latter studies. These tests were chosen because of their predicted accuracy and reproducibility. There were no early quantitative measurements of the D and E fragments and no measurements of fragment Y. Second, there are no estimates of fibrinolysis by thromboelastography (TEG) which has become a very popular technique for looking at fibrinolysis in the 21st century. Previous studies from this laboratory suggested that the old and slower method of TEG provided only quantitative estimates of both F-I and fibrinolysis. Raza and co-authors, more recently, showed poor correlation between TEG results and fibrinolysis as measured by plasmin-antiplasmin complex and D-dimer levels [32]. Although there are many studies that purport successful correlation of fibrinolysis with TEG, there are few studies which compare the accuracy of these TEG results with actual measurements of the fibrinolytic fragments. Such studies need to be done. Third, there were no studies of fibrinolysis made during the short transit time and in the short preoperative period of ongoing resuscitation in these patients who were resuscitated in transit to the operating room. Thus, the correlation of fibrinolysis with fibrinogen levels during this first hour of treatment is not present. One has to assume, based upon prior human and animal studies, that there was increased fibrinolysis during this short interval. This is the only study, however, that monitors FSP from operation through the postoperative period until discharge.

Lastly, there has been great emphasis on the FFP/RBC ratio during resuscitation for severe hemorrhagic shock with the popular teaching that the high ratio (1:1) will improve coagulation and reduce BES needs compared to a low (0.5:1) ratio. Historically, the authors led the trauma community in their defining a protocol for early FFP supplementation when treating hemorrhagic shock [33,34]. This protocol was based upon sequential measurements of coagulation factor content and activity. The authors' current Massive Transfusion Protocol (MTP) reflects these prior scientific studies. The first blood container taken to the emergency department contains 4 units of type O packed cells including type O negative blood for women. When no additional blood is needed, no plasma is infused since the coagulation factors within the interstitial fluid space will rapidly replenish the lost plasma factors. When additional blood is needed, the second container will have 4 units of RBCs and 2 units of FFP; this ratio will then be continued until the MTP is aborted. The end result will be a 0.3:1 ratio for patients requiring ten transfusions and a 0.38:1 ratio for patients requiring 16 transfusions. Serially measured procoagulant levels and procoagulant activities in hundreds of patients treated in the same manner as the patients reported herein have demonstrated excellent coagulation function [2]. Despite all of the literature about the purported benefits of the higher FFP/RBC ratio, there has been only one prospective randomized study testing these benefits.[35] This study demonstrated no difference in mortality at 24 hours or at 30 days when the high 1:1 FFP/RBC ratio is compared to the low 0.5:1 ratio [35]. There is a caveat in this manuscript that there were fewer hemorrhagic deaths in the first 24 hours in those receiving the higher 1:1 ratio; the determination that a patient died from hemorrhage appears to have been made by the first author and was not substantiated in the manuscript by presentation of coagulation factor activity or platelet levels [35]. A subsequent report from this same prospective randomized study demonstrated that the BES resuscitation used during the first 24 hours was not lowered, as was predicted, in the patients receiving the 1:1 FFP/RBC ratio. While this issue continues to be hotly debated, the authors continue to use the MTP that was developed over 30 years ago. Regardless of resuscitation regimen or MTP, these treatment policies should not affect fibrinolysis.

Conclusion

This study demonstrates that fibrinolysis is absent during

resuscitation for hemorrhagic shock both during operation and in the early postoperative interval. Therefore, antifibrinolytic agents at this time are meddlesome. The late rise in F-I to supernormal levels and the associated rise in fibrinolysis needs further study.

Conflict of Interest Statement

The authors state that there are no conflicts of interest regarding funding or financial interests in the subject matter, materials, equipment, or any sources discussed in the manuscript.

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