Non-mechanical Hemorrhage in Severe Liver Injury

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Coagulopathy, or non-mechanical hemorrhage, complicated the operative course of 17 of 33 (51.5%) patients suffering severe liver trauma. The highest incidence of non-mechanical hemorrhage (66.7%) occurred in patients undergoing anatomic lobectomy. Serial hemostatic parameters were assessed and thrombocytopenia was the most striking abnormality in patients with non-mechanical hemorrhage. The degree of thrombocytopenia was directly correlated with the number of blood transfusions administered. The mean operative blood transfusion requirement was significantly greater in patients with non-mechanical hemorrhage, 25.1 ± 2.87 (S.E.M.) units, than in those without, 12.2 ± 1.83 units ($p < 0.001$). The bulk of this transfusion was given before the onset of clinically overt coagulopathy. Massive transfusion of stored blood was felt to be the most important factor in causing non-mechanical hemorrhage. Convincing evidence for disseminated intravascular coagulation was lacking, and abnormal fibrinolysis was infrequent and mild when observed. Although uneventful in most, in six patients non-mechanical hemorrhage resulted in excessive blood transfusion, unnecessary operation or death. Infusions of platelet concentrate, fresh frozen plasma, and fresh blood were used to successfully treat most cases of non-mechanical hemorrhage. In all cases, these components were not started until non-mechanical hemorrhage was clinically apparent. The value of prophylactic use of blood components is stressed. Because of troublesome side effects associated with the use of prothrombin complex concentrates, these agents are contraindicated in patients with severe liver injury. After receiving concentrates, one patient developed severe hypotension leading to ventricular fibrillation, two developed transient thrombocytopenia and two others demonstrated multiple pulmonary microthrombi at autopsy, a finding not observed in autopsied patients not receiving the concentrates.

HEMORRHAGE IS A MAJOR COMPLICATION of severe liver trauma and is the leading cause of death associated with this injury.[15] Bleeding from intra and extra-hepatic vascular structures is mechanical in nature and control requires expeditious and appropriate operation.[14] Coagulopathy, or non-mechanical hemorrhage, frequently occurs in this setting and reported experience cites massive transfusion of stored blood,[10,13,22] disseminated intravascular coagulation,[2,13,21] excessive fibrinolysis[17] and defective clotting factor synthesis[8,17,21] as important determinants in the pathogenesis. The purpose of this study is to review our experience with non-mechanical bleeding associated with severe liver injury in an attempt to elucidate the pathogenesis and formulate rational methods of prevention and treatment.

Methods

Charts from patients with liver injury admitted to the University of Michigan Medical Center and Wayne County General Hospital during the past ten years were reviewed. A classification based on severity of injury was devised. Type I liver injury represents a simple capsular tear. Type II is a minor laceration less than 1 cm in depth. Type III is a major laceration but with viable parenchyma on either side of the wound. Type IV represents a burst injury with major parenchymal disruption. Lastly, Type V signifies major parenchymal injury associated with injuries to the hepatic veins or inferior vena cava.

Patients suffering Types IV and V injuries who initially survived resuscitation and operation formed the basis of this study. Patients who died in the emergency room or during operation were not included since coagulation data were scant. The diagnosis of non-mechanical hemorrhage was based on operative descriptions of generalized oozing from all raw surfaces not correctable by surgical means. These observations were complemented by abnormal coagulation data. In the postoperative period, persistent bleeding from drain, venipuncture, and cutdown sites requiring blood transfusion was considered evidence of non-mechanical hemorrhage when abnormal coagulation studies were present and bleeding was controlled by component therapy.

Perioperative hemostatic parameters were reviewed. These included serial determinations of the platelet

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TABLE 1. *Non-mechanical Hemorrhage*

	Present	Absent
Number	17	16
Age	25.7 ± 15.3 (S.D.) yrs	23.4 ± 7.8 yrs
Sex		
Male	11 (64.7%)	10 (62.5%)
Female	6 (35.3%)	6 (37.5%)
Type of trauma		
Blunt	10 (58.8%)	11 (68.7%)
Penetrating	7 (41.2%)	5 (31.3%)
Associated trauma		
Spleen	5 (29.4%)	4 (25.0%)
Bowel	4 (23.5%)	3 (18.7%)
Bone	4 (23.5%)	5 (31.3%)
CNS	3 (17.7%)	2 (12.5%)
Chest	3 (17.7%)	2 (12.5%)
Arterial	3 (17.7%)	0
Kidney	2 (11.8%)	2 (12.5%)
Multiple trauma	12 (70.6%)	11 (68.7%)
Type of liver injury		
Type IV	11 (64.7%)	14 (87.5%)
Type V	6 (35.3%)	2 (12.5%)
Operations		
Right lobectomy	10 (58.8%)	5 (31.3%)
Left lobectomy	2 (11.8%)	1 (6.2%)
Segmentectomy	3 (17.6%)	8 (50.0%)
Suture	1 (5.9%)	2 (12.5%)
Packing	1 (5.9%)	0
Mortality	7 (41.2%)	0

count, prothrombin time, partial thromboplastin time, thrombin clotting time, fibrinogen level, and euglobulin lysis time. In selected patients fibrin split products titres were monitored to rule out disseminated intravascular coagulation. Blood transfusion requirements were noted and the methods of treating non-mechanical hemorrhage were studied. Patients with non-mechanical hemorrhage were compared to those without to elucidate causative factors.

Results

Thirty-three patients with Types IV or V liver injury initially survived resuscitation and operation. Seventeen (51.5%) had evidence of non-mechanical hemorrhage. In comparing patients with and without non-mechanical hemorrhage, there were no differences in age, sex, or etiology of injury (Table 1). Both groups were comprised mostly of young males with blunt trauma predominating over penetrating injury. In both groups multiple trauma was common. The incidence, types, and severity of associated injuries were similar in both groups, except arterial injuries were more common among those with non-mechanical hemorrhage (Table 1). There were more Type V injuries in the group with non-mechanical hemorrhage. Right hepatic lobectomy was the most commonly performed operation in this group (Table 1). Of 18 patients undergoing anatomic hepatic lobectomy (right and left), 12 (66.7%) developed this complication. The mortality in the group in which non-mechanical hemorrhage was present was 41.2% and zero in those in which it was absent.

Coagulation data in both groups were abnormal with, expectedly, more pronounced changes noted in the group with non-mechanical hemorrhage. Serial prothrombin times were mildly prolonged for the first two to three days postoperative, and then returned towards normal ranges (Fig. 1). Significant differences between the groups were noted only immediately after operation. Serial partial thromboplastin times followed similar trends. The most pronounced coagulation abnormality was thrombocytopenia which occurred in both groups and persisted for the first three days postoperatively (Fig. 2). The group with non-mechanical hemorrhage had a significantly lower mean platelet count immediately following operation. In this group the mean platelet count remained less than 80,000/μL for the first three postoperative days. In all patients, the degree of thrombocytopenia was proportional to the number of blood transfusions with the mean platelet count dropping to 100,000/μL after ten units of blood (Fig. 3).

Additional clotting tests were generally unremarkable and did not serve to differentiate the two groups. Determinations of the euglobulin lysis time were followed in 17 patients and transient abnormalities were noted in two. Serial fibrinogen concentrations were measured in five patients and were modestly reduced in all. Thrombin clotting times were followed in nine patients and were normal. Fibrin split products titres were monitored in three patients and were negative.

The most striking difference between the two groups was the blood transfusion requirements. Intraopera-

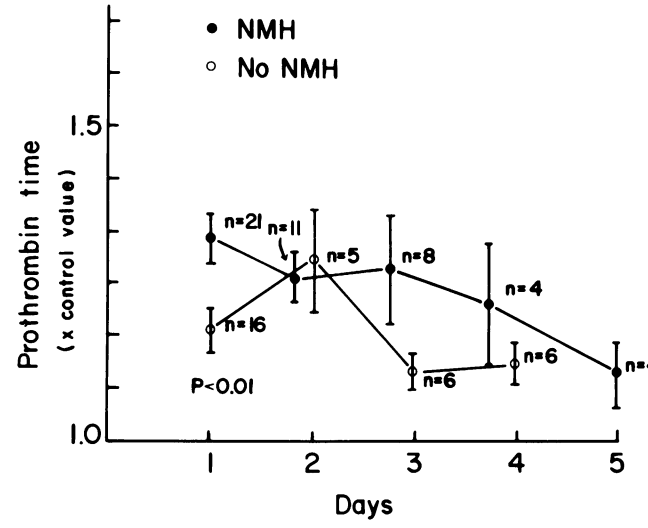

FIG. 1. Mean ± S.E.M. prothrombin value in patients with and without non-mechanical hemorrhage (NMH) on successive days.

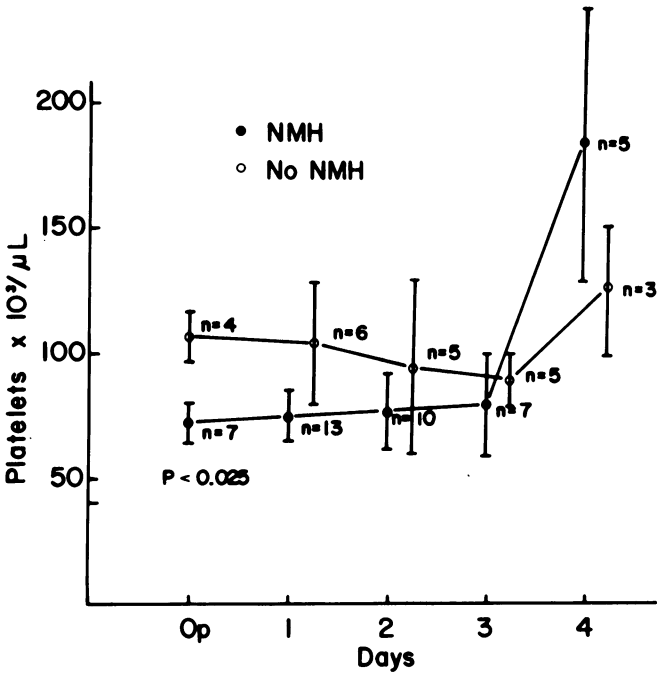

FIG. 2. Mean ± S.E.M. platelet count in patients with and without non-mechanical hemorrhage (NMH) on successive days.

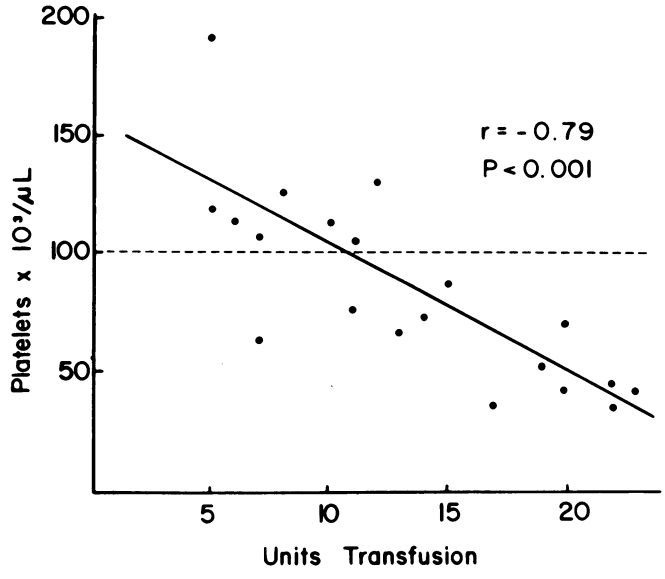

FIG. 3. Platelet count plotted against number of blood transfusions received. Solid line represents fitted regression line, $Y = -5.25x \times 154.6$.

tively, the group suffering non-mechanical hemorrhage received twice the number of blood transfusions (Fig. 4). The mean operative blood transfusion requirement was 25.1 ± 2.87 (S.E.M.) units in patients with non-mechanical hemorrhage compared to 12.2 ± 1.83 units in those without this complication ($p < 0.001$). The bulk of this massive transfusion was given before the onset of clinically overt non-mechanical hemorrhage. The group with non-mechanical hemorrhage also required significantly more transfusions during the first post-operative week (Fig. 4).

A variety of methods was used to treat non-mechanical hemorrhage (Table 2). In all cases these treatments were begun after the onset of non-mechanical hemorrhage. Platelet concentrates were used in most patients, often in combination with fresh frozen plasma. Fresh blood, because of limited availability, was used sparingly. Epsilon-aminocaproic acid was administered to six (35.3%) patients with non-mechanical hemorrhage despite lack of laboratory evidence of abnormal fibrinolysis. Similarly, prothrombin complex concentrates were given to seven (41.2%) patients without clear indications for their use.

The use of prothrombin complex concentrates was associated with troublesome side effects. One patient developed severe hypotension leading to ventricular fibrillation immediately after receiving two vials of Konyne. The agent was infused rapidly (within 2–3 minutes) which is contrary to the manufacturer's advice. Two postoperative patients developed transient

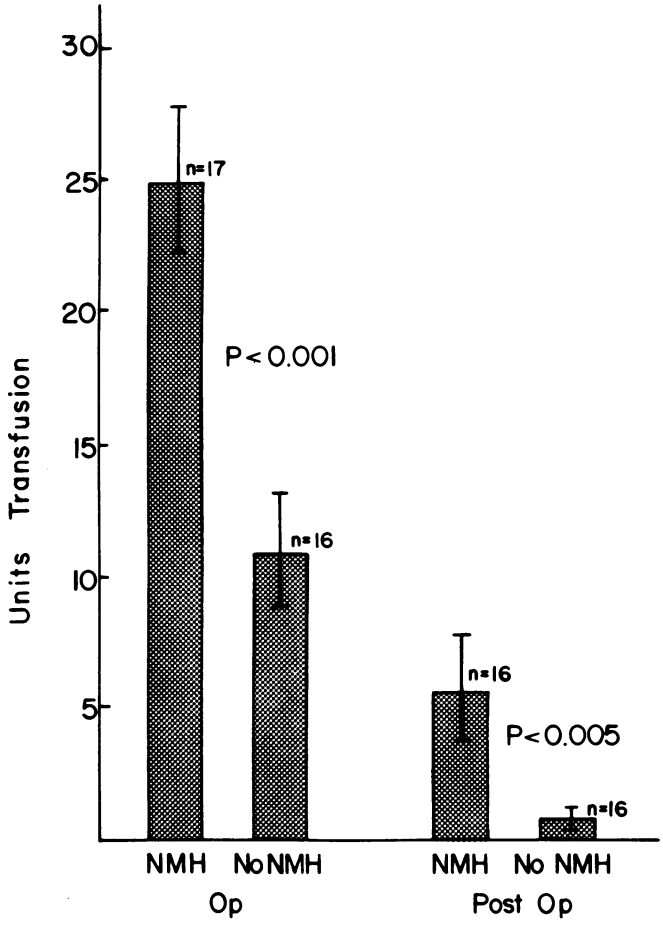

FIG. 4. Blood transfusions administered to patients with and without non-mechanical hemorrhage (NMH) during operation and in the postoperative period.

TABLE 2. *Treatment of Non-mechanical Hemorrhage*

Platelet concentrate	13 (76.5%)
Fresh frozen plasma	7 (41.2%)
Prothrombin complex concentrates	7 (41.2%)
Epsilon-aminocaproic acid	6 (35.3%)
Fresh blood	4 (23.5%)

thrombocytopenia after receiving prothrombin complex concentrates. Neither episode was associated with other coagulation abnormalities and no complications ensued. Two other patients receiving prothrombin complex concentrates demonstrated multiple microthrombi in the pulmonary circulation at autopsy (Fig. 5). These findings were absent in autopsied patients who did not receive these agents.

In 11 of 17 patients with non-mechanical hemorrhage, bleeding was transient, easily controlled and without sequelae. However, in six patients this complication had adverse effects. Two patients required excessive blood transfusion clearly greater than that necessitated by operation alone. In both patients, postoperative bleeding from drain sites required transfusion of more than ten units of blood, and in both, hemostasis was restored with infusions of platelet concentrate given alone or in combination with fresh frozen plasma. In another patient, excessive postoperative bleeding resulted in reoperation which was possibly unnecessary. Despite marked thrombocytopenia, the patient underwent re-exploration during which no major source of hemorrhage was identified. In three patients, bleeding contributed to death in the immediate postoperative period. All three had profuse, uncontrollable oozing from all raw surfaces intraoperatively and were judged not to have a surgically correctable source for bleeding by the attending surgeons. In each, persistent postoperative bleeding and shock resulted in cardiac arrest and death.

Discussion

Non-mechanical hemorrhage or coagulopathy frequently accompanies major hepatic trauma. In this retrospective study, this complication occurred in 51.5% of patients with Types IV and V liver injury. Since patients dying in the emergency room or during operation were not included in this study, this figure is probably conservative. In most patients this complication was transient, easily controlled, and without sequelae; however, in six patients non-mechanical hemorrhage led to excessive transfusion, unnecessary operation, or death.

The etiology of the coagulopathy in this setting has been the object of speculation and study. Most authors cite massive transfusion of stored blood as the major determinant of this complication.[10,13,22] Others have observed disseminated intravascular coagulation,[2,13,21] impaired clotting factor synthesis (especially Factors V and VII)[8,17,21] and excessive fibrinolysis.[17] In the present report, massive blood transfusion was the most striking factor differentiating patients with non-mechanical hemorrhage who received more than twice the number of transfusions than patients without non-mechanical hemorrhage. Thrombocytopenia, the most important determinant of bleeding associated with massive blood transfusion,[20] was the most striking abnormality among the serial tests of clotting function. In patients with non-mechanical hemorrhage, the mean platelet count dropped to 70,000/μL immediately after operation and remained less than 80,000/μL for three days postoperatively (Fig. 2). The inverse correlation between the platelet count and the number of blood transfusions received (Fig. 3) suggests that massive transfusion was responsible for the thrombocytopenia. We did not observe evidence for disseminated intravascular coagulation and abnormal fibrinolysis was unusual and mild when observed. Clotting factor synthesis was not assessed.

Because of the high incidence of non-mechanical

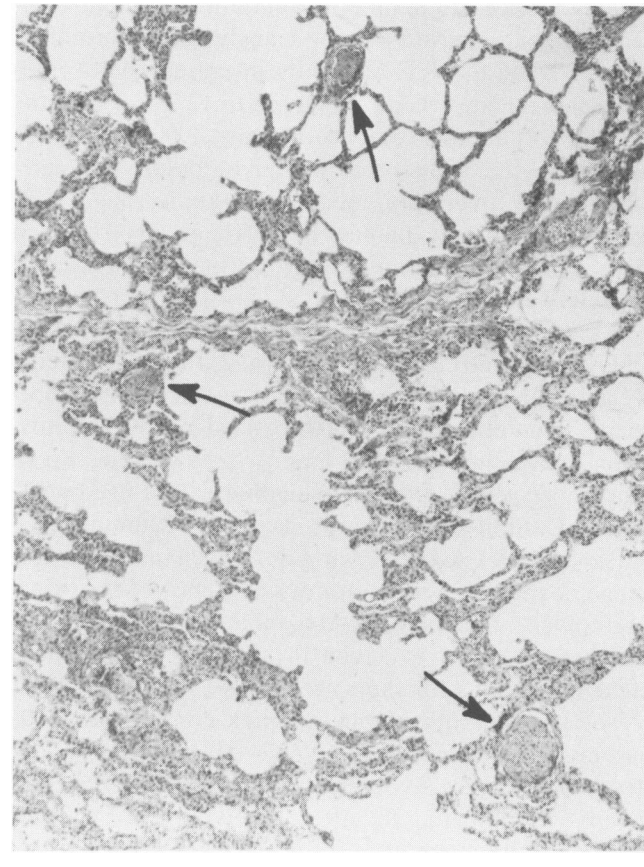

FIG. 5. Pulmonary microthrombi (arrows) seen in patients who received prothrombin complex concentrates.

hemorrhage complicating severe liver injury, methods of prevention are appropriate. Certainly, measures taken to reduce the magnitude of operation and consequent blood loss and transfusion requirement would reduce the frequency of this complication. In the present study, anatomic hepatic lobectomy was performed twice as frequently in the group with non-mechanical hemorrhage with right hepatic lobectomy being the most commonly performed operation in this group. While the appropriateness of operation was not assessed for this study, lesser procedures such as debridement and hepatic artery ligation as advocated by Mays[15] might have been possible and clearly would have decreased the transfusion requirements.

Non-mechanical hemorrhage secondary to massive transfusion is a preventable complication. A consistent feature in treating these patients was that attempts at restoring hemostasis were not begun until after the onset of clinically overt coagulopathy. It would have been more appropriate to have anticipated this complication and prophylactically infused blood components.

The principle underlying the pathogenesis of coagulopathy associated with massive transfusion is dilution. Stored blood greater than 48 hours of age is deficient in platelets and clotting Factors V and VIII, and replacement of the patient's blood with this blood impairs hemostasis. Because of large reserves, deficiencies in the patient's blood of Factors V and VIII are rarely severe. This accounts for the modest prolongation of prothrombin and partial thromboplastin times (infrequently greater than 1½ times control value) encountered in this study. On the other hand, thrombocytopenia, may be marked. Among these patients, the mean platelet count was 100,000/μL after receiving ten units of blood (Fig. 3). Thrombocytopenia of this degree is tolerated in most individuals. However, when combined with mild clotting factor deficiencies in patients with surgical and traumatic wounds in whom further transfusion is anticipated, hemostasis may rapidly decompensate. Correction of thrombocytopenia is the mainstay of treatment directed against bleeding associated with massive transfusion.

In patients in whom massive transfusion might be likely, six to ten units of platelet concentrate should be given after the first ten units of blood have been administered and for every successive ten units of blood. To replenish clotting factor deficiencies, one unit of fresh frozen plasma (which contains normal amounts of all clotting factors) should be given for every three to four units of infused blood. An alternative approach would be to give fresh whole blood in a ratio to stored blood of 1:2–4 units. This would be ideal, but fresh blood is rarely available in emergencies and it is therefore impractical. The important concept is that therapy be started early, before the onset of non-mechanical hemorrhage.

The use of epsilon-aminocaproic acid has been advocated in patients undergoing liver resection.[17] In our experience with severe liver injuries, excessive fibrinolysis is rare. Although we noted no adverse effects from the use of epsilon-aminocaproic acid, others have reported catastrophic thrombotic complications, especially in patients with unrecognized disseminated intravascular coagulation.[4,16] The use of this agent without strong indications is to be condemned.

The liberal use of prothrombin complex concentrates among these patients is of concern. This was most prevalent shortly after 1969 when these agents became commercially available. It appeared that a concentrate of the vitamin K dependent Factors II, VII, IX, and X would be ideal to use in hemorrhaging patients with severe liver injury. Since then a number of complications associated with the use of prothrombin complex concentrates have been reported including hepatitis,[19] anaphylaxis,[7] disseminated intravascular coagulation[3] and other thrombotic events.[1,11] Interestingly, most of the thrombotic complications occurred in patients with liver disease.[11] Prothrombin complex concentrates contain variable amounts of activated factors, particularly IXa and Xa.[1,12] Infusion of these thrombogenic components into patients with liver disease is particularly hazardous because of the liver's important role in clearing activated factors from the circulation.[5] Further, antithrombin III, a natural inhibitor directed against thrombin and other activated factors, has been reported to be low in patients with liver disease.[6]

In our patients the use of prothrombin complex concentrates was associated with complications and manifestations of thrombosis. However, the evidence is suggestive and not conclusive. In the two patients who developed transient thrombocytopenia following infusion of the concentrates, complete hematologic evaluation was not carried out to confirm the presence of disseminated intravascular coagulation. Others have reported transient thrombocytopenia in humans and animals after receiving concentrates and have attributed this to disseminated intravascular coagulation.[9,18] The patient who developed ventricular fibrillation shortly after receiving Konyne is similar in some respects to the case report by Blatt et al.[1] At autopsy, their patient demonstrated widespread fibrin thrombi. Our patient was resuscitated so direct pathologic proof that disseminated thrombosis precipitated this event is lacking. The finding of widespread microthrombi in the lungs of two of our autopsied patients who had received prothrombin complex concentrates was unique in that other autopsied patients not receiving the concentrates did not demonstrate this finding.

However, both of these patients were critically ill, in shock, and receiving multiple blood transfusions, and it would not be unreasonable to attribute the pulmonary microthrombi to other causes.

Despite the absence of direct proof incriminating prothrombin complex concentrates as a causative factor in these complications, the association is bothersome. Because of this and the adverse experience reported by others using these concentrates in patients with liver disease their use in patients with severe liver injury is contraindicated.

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