Original Article

Importance of fibrinogen in dilutional coagulopathy after neurosurgical procedures: A descriptive study

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ABSTRACT

Background and Aims: The routine management of coagulopathy during surgery involves assessing haemoglobin, prothrombin time (PT), activated partial thromboplastin time (aPTT) and platelets. Correction of these parameters involves administration of blood, fresh frozen plasma and platelet concentrates. The study was aimed at identifying the most common coagulation abnormality during neurosurgical procedures and the treatment of dilutional coagulopathy with blood components. **Methods**: During 2 years period, all adult patients undergoing neurosurgical procedures who were transfused two or more units of red cells were prospectively evaluated for the presence of a coagulopathy. PT, aPTT, platelet count and fibrinogen levels were estimated before starting a component therapy. **Results**: After assessing PT, aPTT, platelet count and fibrinogen levels following two or more blood transfusions, thirty patients were found to have at least one abnormal parameter that required administration of a blood product. The most common abnormality was a low fibrinogen level, seen in 26 patients; this was the only abnormality in three patients. No patient was found to have an abnormal PT or aPTT without either the fibrinogen concentration or platelet count or both being low. **Conclusion**: Low fibrinogen concentration was the most common coagulation abnormality found after blood transfusions for neurosurgical procedures.

Key words: Cryoprecipitate, dilutional coagulopathy, fibrinogen, neurosurgery

INTRODUCTION

The early management of blood loss during surgical procedures involves administration of compensatory volumes of crystalloids and colloids. This results in a decrease in the concentration of red blood cells and blood factors necessary for adequate clot formation. In the era of whole blood transfusion, the most common deficiency noticed was thrombocytopaenia, and the solution was the administration of "fresh" blood. With the onset of blood component therapy, this anaemia and dilutional coagulopathy is conventionally dealt with by administering packed red blood cells, fresh frozen plasma (FFP) and platelet concentrates, and a consequence of this is, a deficiency of fibrinogen.[1] The fibrinogen deficiency is not routinely detected because investigation for an acute blood loss and coagulopathy often does not include a fibrinogen assay. Fibrinogen is an important component of the haemostatic process and is essential both for the formation of platelet aggregates and the generation of a sufficiently stable clot. As a rule, fibrinogen replacement is considered only if the fibrinogen level is <100 mg/dL.[2]

The routine evaluation following massive blood transfusion usually includes assessment of haemoglobin, prothrombin time (PT) with the international normalised ratio (INR), activated partial thromboplastin time (aPTT) and platelet count. The subsequent treatment is aimed at correcting the deficient factor with appropriate blood products. We hypothesised that this practice, both with regard to empirical treatment and investigation of a potential coagulopathy caused by blood loss was not paying sufficient attention to fibrinogen. Hence,

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the aim of this study was to detect the most common haematological abnormality arising from dilutional coagulopathy after neurosurgical procedures and to determine the choice of component therapy thereafter.

METHODS

This was a prospective study conducted over a period of 2 years in the Neurosurgical Intensive Care Unit (NICU) of a tertiary care centre. All adult patients who had received two or more units of whole blood or packed cells in the operating room (OR) were screened for the presence of a coagulopathy. PT with INR, aPTT, platelet count and fibrinogen assay were done, before further administration of blood or blood products including FFP, cryoprecipitate or platelets. Fibrinogen assay was done by Von Sclauss assay using the kit from Instrumentation Laboratories, Milan, Italy.

Patients with pre-existing bleeding disorders, on antiplatelet or anticoagulant drugs and those younger than 16 years were excluded from the study.

The triggers for administration of blood components were, INR >1.2, aPTT >34 s, platelet count <100,000/cumm or fibrinogen <200 mg/dL. On detecting an abnormality, respective blood components were replenished with FFP 12 mL/kg, 1 unit of cryoprecipitate for every 10 kg or one bag of platelet for increasing by 10,000.

In view of the dearth of literature on the topic, we undertook a pilot study for 2 years enrolling thirty patients. The study protocol was accepted by the Institutional Review Board [IRB-(EC)-ER-2-19-12].

The primary outcome measure was the incidence of abnormality in bleeding parameters post-operatively following intraoperative dilutional coagulopathy. Secondary outcome measure was the incidence of post-operative haematoma.

Being a descriptive study, we recorded data for 2 years involving thirty patients. The mean and standard deviation were calculated individually for PT, aPTT and fibrinogen values. Since the platelet values were not normally distributed, a median with interquartile range was calculated. The analysis was performed on 29 patients with the following observation removed from analysis due to extreme values; fibrinogen 45 mg/dL, platelet 14,000/cmm, aPTT >3 min and INR >10.

RESULTS

During the study period of 2 years, thirty patients met the inclusion criteria for the study. Predominant male population with a male to female ratio of 20:10 and a mean age of 42 ± 5.2 years of age formed the cohort. The case mix of the study group involved 23 cranial, two spinal and five traumatic brain injury cases. The mean volume infused intraoperatively was 12.80 ± 40.2 L ranging from 6500 to 38600 mL. Eleven patients received various component therapies involving 35 FFPs, 38 cryoprecipitates and five platelets. Fibrinogen deficiency with mean levels of 145.38 ± 47.09 mg% was the most common abnormality following dilutional coagulopathy (ranging from 54.6 to 250 mg%). Twenty-six patients (87%) developed hypofibrinogenaemia and this was the only abnormality in three patients. Four patients had only a low platelet count, three had an isolated fibrinogen deficiency, and all other patients had a combination of abnormalities. The mean aPTT was 31.62 ± 10.69 s (ranging from 20 to 50.5) and INR of 1.27 ± 0.3 (ranging from 0.93 to 2.03). Median platelet value observed was 82,500/cmm with IQR of 53,500, 123,500 (ranging from 30,000 to 24,7000/cmm). No patient was found to have a high aPTT or INR value unless either the platelet count, fibrinogen level or both were abnormal. In one patient who was transfused almost 4 times her blood volume still did not develop a severe coagulopathy because of adequate replacement of blood component during the surgery, but she died of sepsis on the second post-operative day. Two patients required reoperation for post-operative haematomas; one had very low level of (45 mg%) fibrinogen as well as gross abnormalities of all other tests, and the other was transfused two packs of whole blood intraoperatively leading to thrombocytopaenia but adequate levels of fibrinogen.

DISCUSSION

This observational study stratifies the role of individual component therapy following dilutional coagulopathy in neurosurgical pathologies. Fibrinogen is the first component to drop and is always present with other coagulation abnormalities in cases of dilutional coagulopathy. If not replaced adequately hypofibrinogenaemia following neurosurgical procedures leads to catastrophic post-operative complications as emphasised in our findings.[3] Two of the patients needed recraniotomy to evacuate post-operative haematomas (before the NICU protocol was altered) and this is evidence of the need for

quick and adequate transfusion of cryoprecipitate. Goh *et al*. observed a hypocoagulable state with increased disseminated intravascular coagulation type mechanisms or fibrinolysis in patients with post-operative haematomas.[4] However, there is paucity of literature and recommendations on transfusion trigger for blood and blood products after neurosurgical procedures. Our work strengthens the earlier hypotheses that fibrinogen assay should be an integral component of coagulation workup. Not investigating for it would lead to inability to diagnose coagulation abnormality in 10% of cases. Preemptive correction of the likely cause of bleeding would have immense repercussions on surgical procedure where controlled blood loss will improve the ease, speed and quality of technique. This practice will improve patient safety and complications related to increase blood transfusion.

The pathology underlying dilutional coagulopathy is impairment of the final step of fibrin polymerisation in the haemostatic process. Polymerisation of fibrinogen and thus total clot strength has been found to be impaired even at moderate blood loss and infusion of about 1500–2000 mL of colloids.[5] In the cohort of trauma victims, replacement of fibrinogen deficiency has been found to have survival benefits with a direct correlation between the amount of fibrinogen replaced and reduction in mortality.[5-8]

Although the conventional trigger for fibrinogen replacement is 100 mg/dL, we opted to increase this to 200 mg/dL as bleeding into the intracranial cavity is not a matter of excessive bleeding into a drain and replacement, as in most other surgeries. This was in accordance with the latest European trauma guidelines recommending fibrinogen replacement for plasma levels <150–200 mg/dL.[9] An *in vitro* study too revealed the optimal concentration of fibrinogen for adequate clot formation to be 200 mg/dL, and complete correction of coagulation on thromboelastography needed a concentration >250 mg/dL.[10] The benefit of fibrinogen replacement in a porcine model of dilutional coagulopathy (attained by replacement of blood with gelatin solution) was seen as improved clot formation and decreased blood loss even after 65% dilution.[11] The most common derangement of coagulation found in our series was a low fibrinogen level in 87% of patients and in three patients, it was the only abnormality detected.

Harr *et al*. evaluated the role of each component of clot strength in trauma patients using thromboelastogram.[12] They found only fibrinogen component of clot strength to improve linearly with increasing fibrinogen level whereas, increase in platelet count decreased the platelet contribution to clot strength.[12] If we acknowledge that low fibrinogen could result in an unstable clot, then not testing for fibrinogen would have resulted in missing 10% of post-operative coagulopathies in our series.

Contrary to earlier recommendations in massive transfusions to administer FFP and increase levels of clotting and antifibrinolytic factors, our results suggest transfusing cryoprecipitate upfront. FFP contains anticoagulants such as antithrombin that are necessary to prevent excessive action of thrombin and activated factor X that would otherwise result in disseminated intravascular coagulation.[13] However, it is not a good source of fibrinogen replacement. FFP administered at 10–15 mL/kg increases fibrinogen by 40 mg/dL and 30 ml/kg of FFP increases fibrinogen by 100 mg/dL,[14] making it extremely difficult to increase fibrinogen concentration with FFP alone, unless very large volumes are used. On the other hand, 15 mL of cryoprecipitate for every 10 kg body weight increases the fibrinogen level by 50 mg/dL.[15] Therefore, increasing the fibrinogen level by 100 mg/dL in a 60 kg patient would require 1800 ml of FFP or 180 ml of cryoprecipitate.

The mean fibrinogen level in the series was only 145.38 mg%. After observing the trend from the first few patients in this series, the NICU protocol was changed to mandate administration of one unit of cryoprecipitate for every 10 kg body weight empirically in any patient suspected to have a dilutional coagulopathy, without waiting for the results of laboratory sets. This might explain the comparatively low incidence of post-operative haemorrhage in our series. In view of patient safety, these results have also led to a change of practice in the OR, with early administration of cryoprecipitate in the event of significant blood loss. The derangement of coagulation in a dilutional coagulopathy is attributed to the decreased concentration of procoagulant factors, but this is accompanied by an equal dilution of natural anticoagulant factors in the blood, and might be the reason that the PT and aPTT are frequently normal.[16] As mentioned earlier when implemented in the OR this would translate into better haemostasis and improve patient safety with lesser bleeding intra-operatively.

In the absence of any such study previously, a systematic analysis on the subject is not possible. Having raised a

hypotheses not well-recognised earlier; our study has the limitation of small population size, observational nature and single centered. However, it is the first step towards early recognition of coagulopathy and hypofibrinogenaemia in elective neurosurgical patients. A large well-designed, multicentric comparative study should be the way forward for making proper recommendations and guidelines.

CONCLUSION

This study emphasises the importance of evaluating fibrinogen level for suspected dilutional coagulopathy after neurosurgical procedures and administering cryoprecipitate preemptively for suspected dilutional coagulopathy. Larger trials in this cohort of patients are needed to formulate recommendations in the often seen scenario of dilutional coagulopathy after neurosurgical procedures.

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Conflicts of interest

There are no conflicts of interest.

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